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(51) International Patent Classification ⁶ : C07D 401/12, 401/14, A61K 31/44 // (C07D 401/12, 233:00, 213:00)		A1	(11) International Publication Number: WO 98/15547 (43) International Publication Date: 16 April 1998 (16.04.98)
(21) International Application Number: PCT/EP97/05231 (22) International Filing Date: 24 September 1997 (24.09.97) (30) Priority Data: 08/731,128 9 October 1996 (09.10.96) US (71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE). (72) Inventors: KOCHANNY, Monica, J.; 193 Irwin Street, San Rafael, CA 94901 (US). MORRISSEY, Michael, M.; 129 Alta Vista Way, Danville, CA 94806 (US). NG, Howard, P.; 20 Dias Court, El Sobrante, CA 94803 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: THIO ACID DERIVED MONOCYCLIC N-HETEROCYCLICS AS ANTICOAGULANTS			
(57) Abstract This invention is directed to monocyclic N-heterocyclics which are substituted by acyclic or cyclic thio derivatives which are useful as anti-coagulants. This invention is also directed to pharmaceutical compositions containing the compounds of the invention, and methods of using the compounds to treat disease-states characterized by thrombotic activity.			

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THIO ACID DERIVED MONOCYCLIC *N*-HETEROCYCLICS AS ANTICOAGULANTS

Field of the Invention

The present invention is directed to monocyclic *N*-heterocyclics which are substituted by acyclic and cyclic thio acid derivatives, and their pharmaceutically acceptable salts, which inhibit the enzyme, factor Xa, thereby being useful as anti-coagulants. It also relates to pharmaceutical compositions containing the derivatives or their pharmaceutically acceptable salts, and methods of their use.

BACKGROUND OF THE INVENTION

Factor Xa is a member of the trypsin-like serine protease class of enzymes. A one-to-one binding of factors Xa and Va with calcium ions and phospholipid forms the prothrombinase complex which converts prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin which polymerizes to form insoluble fibrin.

In the coagulation cascade, the prothrombinase complex is the convergent point of the intrinsic (surface activated) and extrinsic (vessel injury-tissue factor) pathways (*Biochemistry* (1991), Vol. 30, p. 10363; and *Cell* (1988), Vol. 53, pp. 505-518). The model of the coagulation cascade has been refined further with the discovery of the mode of action of tissue factor pathway inhibitor (TFPI) (*Seminars in Hematology* (1992), Vol. 29, pp. 159-161). TFPI is a circulating multi-domain serine protease inhibitor with three Kunitz-type domains which competes with factor Va for free factor Xa. Once formed, the binary complex of factor Xa and TFPI becomes a potent inhibitor of the factor VIIa and tissue factor complex.

Factor Xa can be activated by two distinct complexes, by tissue factor-VIIa complex on the "Xa burst" pathway and by the factor IXa-VIIIa complex (TENase) of the "sustained Xa" pathway in the coagulation cascade. After vessel injury, the "Xa burst" pathway is activated *via* tissue factor (TF). Up regulation of the coagulation cascade occurs *via* increased factor Xa production *via* the "sustained Xa" pathway. Down regulation of the coagulation cascade occurs with the formation of the factor Xa-TFPI complex, which not only removes factor Xa but also inhibits further factor formation *via* the "Xa burst" pathway. Therefore, the coagulation cascade is naturally regulated by factor Xa.

The primary advantage of inhibiting factor Xa over thrombin in order to prevent coagulation is the focal role of factor Xa versus the multiple functions of thrombin.

Thrombin not only catalyzes the conversion of fibrinogen to fibrin, factor VIII to VIIIa, factor V to Va, and factor XI to XIa, but also activates platelets, is a monocyte chemotactic factor, and mitogen for lymphocytes and smooth muscle cells. Thrombin activates protein C, the *in vivo* anti-coagulant inactivator of factors Va and VIIIa, when
5 bound to thrombomodulin. In circulation, thrombin is rapidly inactivated by antithrombin III (ATIII) and heparin cofactor II (HCII) in a reaction which is catalyzed by heparin or other proteoglycan-associated glycosaminoglycans, whereas thrombin in tissues is inactivated by the protease, nexin. Thrombin carries out its multiple cellular activation functions through a unique "tethered ligand" thrombin receptor (*Cell* (1991),
10 Vol. 64, p. 1057), which requires the same anionic binding site and active site used in fibrinogen binding and cleavage and by thrombomodulin binding and protein C activation. Thus, a diverse group of *in vivo* molecular targets compete to bind thrombin and the subsequent proteolytic events will have very different physiological consequences depending upon which cell type and which receptor, modulator, substrate
15 or inhibitor binds thrombin.

Published data with the proteins antistasin and tick anti-coagulant peptide (TAP) demonstrate that factor Xa inhibitors are efficacious anti-coagulants (*Thrombosis and Haemostasis* (1992), Vol. 67, pp. 371-376; and *Science* (1990), Vol. 248, pp. 593-596).

20 The active site of factor Xa can be blocked by either a mechanism-based or a tight binding inhibitor (a tight binding inhibitor differs from a mechanism-based inhibitor by the lack of a covalent link between the enzyme and the inhibitor). Two types of mechanism-based inhibitors are known, reversible and irreversible, which are distinguished by ease of hydrolysis of the enzyme-inhibitor link (*Thrombosis Res* (1992),
25 Vol. 67, pp. 221-231; and *Trends Pharmacol. Sci.* (1987), Vol. 8, pp. 303-307). A series of guanidino compounds are examples of tight-binding inhibitors (*Thrombosis Res.* (1980), Vol. 19, pp. 339-349). Arylsulfonyl-arginine-piperidine-carboxylic acid derivatives have also been shown to be tight-binding inhibitors of thrombin (*Biochem.* (1984), Vol. 23, pp. 85-90), as well as a series of arylamidine-containing compounds,
30 including 3-amidinophenylaryl derivatives (*Thrombosis Res.* (1983), Vol. 29, pp. 635-642) and bis(amidino)benzyl cycloketones (*Thrombosis Res.* (1980), Vol. 17, pp. 545-548). However, these compounds demonstrate poor selectivity for factor Xa.

Related Disclosures

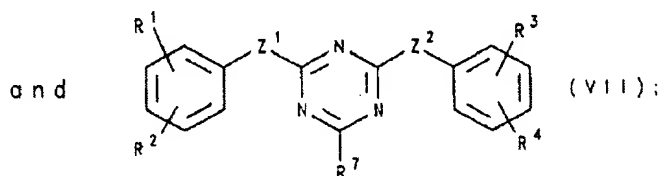
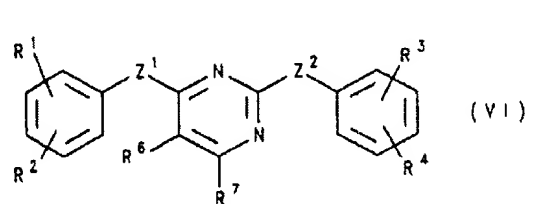
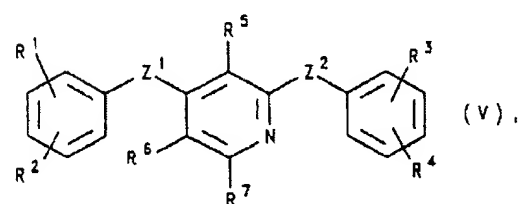
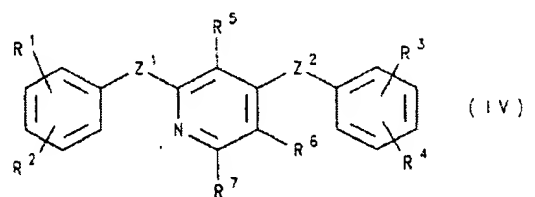
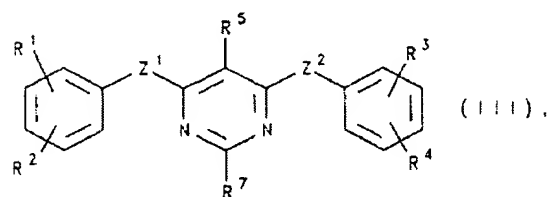
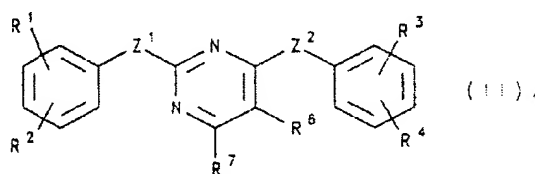
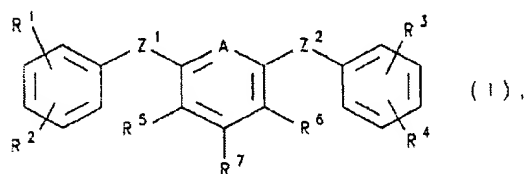
European Published Patent Application 0 540 051 (Nagahara *et al.*) describes aromatic amidine derivatives which are stated to be capable of showing a strong anticoagulant effect through reversible inhibition of factor Xa.

- 5 The synthesis of α,α' -bis(amidinobenzylidene)cycloalkanones and α,α' -bis(amidinobenzyl)cycloalkanones is described in *Pharmazie* (1977), Vol. 32, No. 3, pp. 141-145. These compounds are disclosed as being serine protease inhibitors.

SUMMARY OF THE INVENTION

- 10 This invention is directed to compounds or their pharmaceutically acceptable salts which inhibit human factor Xa and are therefore useful as pharmacological agents for the treatment of disease-states characterized by thrombotic activity.

Accordingly, in one aspect, this invention provides compounds selected from the group consisting of the following formulae:



wherein:

A is $-C(R^8)=$ or $-N=$;

Z^1 and Z^2 are independently $-O-$, $-N(R^{12})-$, $-OCH_2-$ or $-S(O)_n$ (where n is 0 to 2);

R^1 and R^4 are each independently hydrogen, halo, alkyl, nitro, $-OR^{12}$, $-C(O)OR^{12}$,

5 $-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{12}$, or $-N(H)S(O)_2R^{15}$;

R^2 is $-C(NH)NH_2$, $-C(NH)N(H)OR^{12}$, $-C(NH)N(H)C(O)OR^{15}$, $-C(NH)N(H)C(O)R^{12}$,

$-C(NH)N(H)S(O)_2R^{15}$, or $-C(NH)N(H)C(O)N(H)R^{12}$;

R^3 is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, guanidino, $-OR^{12}$, $-C(NH)NH_2$,

$-C(NH)N(H)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})R^{13}$, $-CH(OH)C(O)N(R^{12})R^{13}$,

10 $-N(R^{12})R^{13}$, $-R^{14}-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-N(R^{12})C(O)R^{12}$,

(1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl

(optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 and R^6 are independently hydrogen, halo, alkyl, haloalkyl, nitro, $-N(R^{12})R^{13}$,

15 $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-C(O)N(R^{12})CH_2C(O)N(R^{12})R^{13}$,

$-N(R^{12})C(O)N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{13}$, $-N(R^{12})S(O)_2R^{15}$, or

$-N(R^{12})C(O)N(R^{12})-CH_2C(O)N(R^{12})R^{13}$;

R^7 is $-S(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 to 2 and m is 1 to 4) or

$-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 to 2 and p is 0 to 4), with the proviso

20 that the carbon atom bonded to the sulfur atom in either of these radicals can not be bonded to another hetero atom;

R^8 is hydrogen, alkyl or halo;

each R^9 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl,

cycloalkyl, cycloalkylalkyl, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$,

25 $-R^{14}-C(O)N(R^{12})R^{13}$, $-C(O)-R^{14}-N(R^{12})R^{13}$, $-R^{14}-C(O)-R^{14}-N(R^{12})R^{13}$, $-C(O)R^{12}$,

$-R^{14}-C(O)R^{12}$, $-C(O)N(R^{12})N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})N(R^{12})R^{13}$,

$-C(R^{12})(OR^{12})-R^{14}-N(R^{12})(R^{13})$, $-R^{14}-C(R^{12})(OR^{12})-R^{14}-N(R^{12})(R^{13})$,

$-C(R^{12})(OR^{12})C(O)OR^{12}$, $-R^{14}-C(R^{12})(OR^{12})C(O)OR^{12}$, $-C(R^{12})(C(O)OR^{12})_2$,

$-R^{14}-C(R^{12})(C(O)OR^{12})_2$, $-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$,

30 $-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-C(R^{12})(OR^{12})R^{13}$, $-R^{14}-C(R^{12})(OR^{12})R^{13}$,

$-N(R^{12})R^{13}$, $-R^{14}-N(R^{12})R^{13}$, $-N(R^{12})C(O)OR^{15}$, $-R^{14}-N(R^{12})C(O)OR^{15}$,

$-N(R^{12})C(O)R^{13}$, $-R^{14}-N(R^{12})C(O)R^{13}$, $-N(R^{12})C(NR^{12})R^{15}$,

$-R^{14}-N(R^{12})C(NR^{12})R^{15}$, $-N(R^{12})S(O)_2R^{15}$, $-R^{14}-N(R^{12})S(O)_2R^{15}$,

$-N(R^{12})C(O)N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(O)N(R^{12})R^{13}$, $-N(R^{12})C(NR^{12})N(R^{12})R^{13}$,

- $-R^{14}-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-N(R^{12})C(NR^{12})N(R^{12})N(R^{12})R^{13}$,
 $-R^{14}-N(R^{12})C(NR^{12})N(R^{12})N(R^{12})R^{13}$, $-N(R^{12})-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$,
 $-R^{14}-N(R^{12})-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-N(R^{12})S(O)R^{13}$,
 $-R^{14}-N(R^{12})S(O)R^{13}$, $-OR^{12}$, $-R^{14}-OR^{12}$, $-O-N(R^{12})C(NR^{12})N(R^{12})R^{13}$,
5 $-R^{14}-O-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-OS(O)_2OR^{12}$, $-R^{14}-OS(O)_2OR^{12}$,
 $-P(O)(OR^{12})R^{13}$, $-R^{14}-P(O)(OR^{12})R^{13}$, $-OP(O)(OR^{12})_2$, $-R^{14}-OP(O)(OR^{12})_2$,
 $-P(O)(OR^{12})_2$, $-R^{14}-P(O)(OR^{12})_2$, $-SR^{12}$, $-R^{14}-SR^{12}$, $-C(SR^{12})(R^{12})C(O)OR^{12}$
 (where n is 0 to 2), $-R^{14}-C(SR^{12})(R^{12})C(O)OR^{12}$ (where n is 0 to 2),
 $-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0
10 to 2), $-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where
 n is 0 to 2), $-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2),
 $-R^{14}-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2),
 $-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$
 (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
15 $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$,
 $-SC(O)N(R^{12})R^{13}$, $-R^{14}-SC(O)N(R^{12})R^{13}$, $-SC(S)N(R^{12})R^{13}$, $-R^{14}-SC(S)N(R^{12})R^{13}$,
 $-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)OR^{12}$,
 $-R^{14}-S(O)_2OR^{12}$, $-R^{14}-S(O)_2N(R^{12})R^{13}$, $-R^{14}-S(O)(NR^{12})R^{13}$;
20 or each R^9 is aryl (optionally substituted by one or more substituents selected from the
 group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$,
 $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$,
 $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
 or each R^9 is aralkyl (where the aryl radical is optionally substituted by one or more
25 substituents selected from the group consisting of alkyl, halo, haloalkyl,
 haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$,
 $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
 or each R^9 is aralkenyl (where the aryl radical is optionally substituted by one or more
30 substituents selected from the group consisting of alkyl, halo, haloalkyl,
 haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$,
 $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
 or each R^9 is heterocyclyl (optionally substituted by one or more substituents selected
 from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, aralkyl,
 $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$,

$-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$;

or each R^9 is heterocyclalkyl (where the heterocycl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{S}(\text{O})_q\text{R}^{15}$ (where q is 1 or 2), $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$);

or each R^9 is heterocyclalkenyl (where the heterocycl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{S}(\text{O})_q\text{R}^{15}$ (where q is 1 or 2), $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$);

or each R^9 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{S}(\text{O})_q\text{R}^{15}$ (where q is 1 or 2), $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$);

or each R^9 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{S}(\text{O})_q\text{R}^{15}$ (where q is 1 or 2), $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$);

each R^{10} is independently hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

or R^9 and R^{10} together form a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{12}$, or $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$;

R^{11} is $-\text{C}(\text{O})\text{OR}^{12}$ or $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$;

each R^{12} and R^{13} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{14} is an alkylene or alkylidene chain;

R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and

R^{16} is a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$;

or R^{16} is a mono-, bi- or tricyclic heterocyclic ring system containing from 3 to 15 ring members including carbon and 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur atoms, wherein the carbon, nitrogen and sulfur atoms may be optionally oxidized and the nitrogen atoms may be optionally quarternized, and wherein the heterocyclic ring system may be partially or fully saturated or aromatic and is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides compositions useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound of the invention as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, this invention provides a method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

In another aspect, this invention provides a method of treating a human having a disease-state alleviated by the inhibition of factor Xa, which method comprises

administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

In another aspect, this invention provides a method of inhibiting human factor Xa *in vitro* or *in vivo* by the administration of a compound of the invention.

5

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting
10 solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

"Alkenyl" refers to a straight or branched chain unsaturated monovalent radical
15 consisting solely of carbon and hydrogen atoms, having from one to six carbon atoms, wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

"Alkynyl" refers to a straight or branched chain monovalent or divalent radical
20 consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl, and the like.

"Alkoxy" refers to a radical of the formula -OR_a where R_a is alkyl as defined
25 above, *e.g.*, methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (*iso*-propoxy), *n*-butoxy, *n*-pentoxy, 1,1-dimethylethoxy (*t*-butoxy), and the like.

"Alkylene chain" refers to straight or branched chain divalent radical consisting
solely of carbon and hydrogen atoms, containing no unsaturation and having from one to six carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like.

30 "Alkylidene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from one to six carbon atoms, wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule; *e.g.*,

ethylidene, propylidene, *n*-butylidene, and the like.

"Aryl" refers to a phenyl or naphthyl radical.

"Aralkyl" refers to a radical of the formula $-R_bR_c$ where R_b is an alkylene chain, as defined above, substituted by R_c , an aryl radical, as defined above, *e.g.*, benzyl.

5 "Aralkenyl" refers to a radical of the formula $-R_dR_c$ where R_d is an alkylidene chain, as defined above, substituted by R_c , an aryl radical, as defined above, *e.g.*, 2-phenylethylidenyl.

"Aryloxy" refers to a radical of the formula $-OR_c$ where R_c is an aryl radical as defined above, *e.g.*, phenoxy and naphthoxy.

10 "Aralkoxy" refers to a radical of the formula $-OR_e$ where R_e is an aralkyl radical as defined above, *e.g.*, benzyloxy, and the like.

"Amidino" refers to the radical $-C(NH)NH_2$.

"Cycloalkyl" refers to a stable 3- to 10-membered monocyclic radical which is saturated, and which consists solely of carbon and hydrogen atoms, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

15 "Cycloalkylalkyl" refers to a radical of the formula $-R_bR_f$ where R_b is an alkylene chain, as defined above, and R_f is a cycloalkyl radical as defined above, *e.g.*, cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, and the like.

"Carbocyclic ring system" refers to a stable 3- to 15-membered ring radical consisting solely of carbon and hydrogen atoms. For purposes of this invention, the carbocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring system, which may include bridged ring systems, and the ring system may be partially or fully saturated or aromatic, and the carbon atoms in the ring system may be optionally oxidized. Examples of such carbocyclic ring system radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentyl, norbornane, norbornene, adamantyl, bicyclo[2.2.2]octane and the like.

25 "Dialkylamino" refers to a radical of the formula $-N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

30 "Dialkylaminocarbonyl" refers to a radical of the formula $-C(O)N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like.

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

5 "Haloalkoxy" refers to a radical of the formula $-OR_g$ where R_g is an haloalkyl radical as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3-bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like.

10 "Haloalkenyl" refers to an alkenyl radical as defined above, that is substituted by one or more halo radicals, *e.g.*, bromoethenyl, 3-trifluoroprop-1-enyl, bromobut-1-enyl, chloropent-1-enyl, bromopenta-1,4-dienyl, and the like.

"Heterocyclyl" refers to a stable 3- to 10-membered monocyclic or bicyclic radical which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and wherein the nitrogen, carbon or sulfur atoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclyl radical may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclyl radicals include, but are not limited to, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 20 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazoliny, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 25 octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieryl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl.

30 "Heterocyclylalkyl" refers to a radical of the formula $-R_bR_h$ where R_b is an alkylene chain, as defined above, and R_h is a heterocyclyl radical as defined above, *e.g.*, indolinylmethyl or imidazolylmethyl, and the like.

"Heterocyclylalkenyl" refers to a radical of the formula $-R_dR_h$ where R_d is an alkylidene chain, as defined above, and R_h is a heterocyclyl radical as defined above, *e.g.*, indolinylmethyl or imidazolylmethylenyl, and the like.

"Adamantylalkyl" refers to a radical of the formula $-R_bR_i$ where R_b is an alkylene chain, as defined above, and R_i is an adamantyl radical, *e.g.*, adamantylmethyl, 2-adamantylethyl, and the like.

"Heterocyclic ring system" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclic ring system radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the ring system may be partially or fully saturated or aromatic. The heterocyclic ring system radical may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic ring system radicals include, but are not limited to, aziridinyl, azetidiny, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolinyl, octahydroisoindolinyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, decahydroisoquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 2-azabicyclo[2.2.2]heptyl and oxadiazolyl. Preferred heterocyclic ring system radicals for this invention are 2-oxopiperazinyl, tetrahydroquinolinyl, dihydroquinolinyl, thiazolidinyl, and quinuclidinyl.

"(1,2)-Imidazolyl" refers to an imidazolyl radical attached at either the 1- or 2-position.

"(1,2)-Imidazolinyl" refers to a 4,5-dihydroimidazolyl radical attached at either the 1- or the 2-position.

"Monoalkylamino" refers to a radical of the formula $-NHR_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylamino, ethylamino, propylamino, and the like.

"Monoalkylaminocarbonyl" refers to a radical of the formula $-C(O)NHR_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylaminocarbonyl, ethylaminocarbonyl,

propylaminocarbonyl, and the like.

"(1,2)-Tetrahydropyrimidinyl" refers to a tetrahydropyrimidinyl radical attached at either the 1- or 2-position.

"Optional" or "optionally" means that the subsequently described event of
5 circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

10 "Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the
15 like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which
20 retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred
25 inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine,
30 ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine,

dicyclohexylamine, choline and caffeine.

"Therapeutically effective amount" refers to that amount of a compound of formula (I) which, when administered to a human in need thereof, is sufficient to effect treatment, as defined below, for disease-states characterized by thrombotic activity.

- 5 The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease-state and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

- 10 "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by thrombotic activity, and includes:

(i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it;

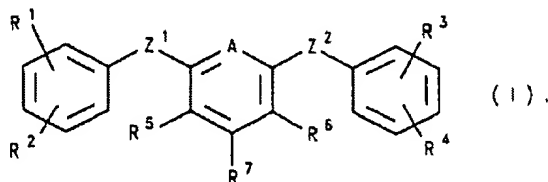
(ii) inhibiting the disease-state, *i.e.*, arresting its development; or

- 15 (iii) relieving the disease-state, *i.e.*, causing regression of the disease-state.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

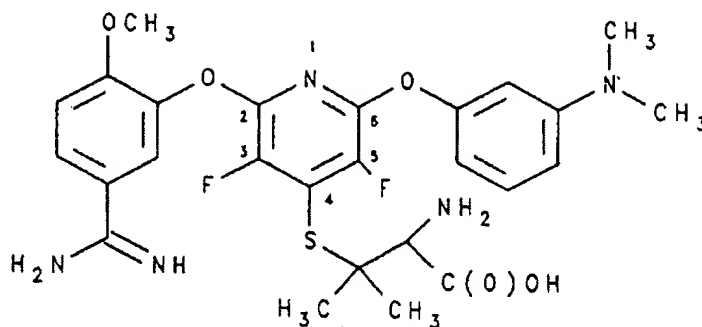
- 20 The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

- 25 The nomenclature used herein is a modified form of the I.U.P.A.C. system wherein the compounds of the invention are named as derivatives of benzamidine. For example, a compound of the invention selected from formula (I):



wherein A is -N-; Z¹ and Z² are both -O-; R¹ is methoxy; R² is -C(NH)NH₂; R³ is dimethylamino; R⁴ is hydrogen; R⁵ and R⁶ are both fluoro; and R⁷ is

-S-C(CH₃)₂-C(H)(NH₂)C(O)OH; *i.e.*, the compound of the following formula:



is named herein as 4-methoxy-3-[(4-{(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-6-(3-dimethylaminophenoxy)-3,5-difluoropyridin-2-yl)oxy}benzamidine.

Utility and Administration

5 A. Utility

The compounds of the invention are inhibitors of factor Xa and therefore useful in disease-states characterized by thrombotic activity based on factor Xa's role in the coagulation cascade (see Background of the Invention above). A primary indication for the compounds is prophylaxis for long term risk following myocardial infarction.

- 10 Additional indications are prophylaxis of deep vein thrombosis (DVT) following orthopedic surgery or prophylaxis of selected patients following a transient ischemic attack. The compounds of the invention may also be useful for indications in which coumarin is currently used, such as for DVT or other types of surgical intervention such as coronary artery bypass graft and percutaneous transluminal coronary angioplasty.
- 15 The compounds are also useful for the treatment of thrombotic complications associated with acute promyelocytic leukemia, diabetes, multiple myelomas, disseminated intravascular coagulation associated with septic shock, purpura fulminans associated infection, adult respiratory distress syndrome, unstable angina, and thrombotic complications associated with aortic valve or vascular prosthesis. The
- 20 compounds are also useful for prophylaxis for thrombotic diseases, in particular in patients who have a high risk of developing such disease.

In addition, the compounds of the invention are useful as *in vitro* and *in vivo* diagnostic reagents for selectively inhibiting factor Xa without inhibiting other components of the coagulation cascade.

B. Testing

The primary bioassays used to demonstrate the inhibitory effect of the compounds of the invention on factor Xa are simple chromogenic assays involving only serine protease, the compound of the invention to be tested, substrate and buffer (see, *e.g.*, *Thrombosis Res.* (1979), Vol. 16, pp. 245-254). For example, four tissue human serine proteases can be used in the primary bioassay, free factor Xa, prothrombinase, thrombin (IIa) and tissue plasminogen activator (tPA). The assay for tPA has been successfully used before to demonstrate undesired side effects in the inhibition of the fibrinolytic process (see, *e.g.*, *J. Med. Chem.* (1993), Vol. 36, pp. 314-319).

Another bioassay useful in demonstrating the utility of the compounds of the invention in inhibiting factor Xa demonstrates the potency of the compounds against free factor Xa in citrated plasma. For example, the anticoagulant efficacy of the compounds of the invention will be tested using either the prothrombin time (PT), or activated partial thromboplastin time (aPTT) while selectivity of the compounds is checked with the thrombin clotting time (TCT) assay. Correlation of the K_i in the primary enzyme assay with the K_i for free factor Xa in citrated plasma will screen against compounds which interact with or are inactivated by other plasma components. Correlation of the K_i with the extension of the PT is a necessary *in vitro* demonstration that potency in the free factor Xa inhibition assay translates into potency in a clinical coagulation assay. In addition, extension of the PT in citrated plasma can be used to measure duration of action in subsequent pharmacodynamic studies.

For further information on assays to demonstrate the activity of the compounds of the invention, see R. Lottenberg *et al.*, *Methods in Enzymology* (1981), Vol. 80, pp. 341-361, and H. Ohno *et al.*, *Thrombosis Research* (1980), Vol. 19, pp. 579-588.

C. General Administration

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out *via* any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, *etc.*

Generally, depending on the intended mode of administration, the

5 pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical
10 excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease-state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention, or a pharmaceutically acceptable salt
15 thereof, is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release
20 formulations and the like.

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia,
25 polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like..

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, *e.g.*, polyoxyethylene glycols and polyethylene glycols (PEG), *e.g.*, PEG 1000 (96%) and PEG
30 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, *etc.*, a compound(s) of the invention (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol,

ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan

5 monolaurate, triethanolamine oleate, butylated hydroxytoluene, *etc.*

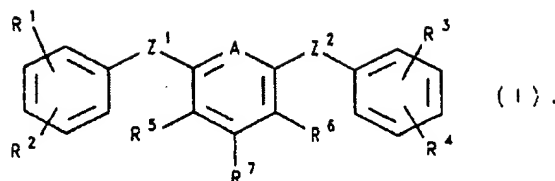
Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a
10 compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state alleviated by the inhibition of factor Xa in accordance with the teachings of this invention.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a
15 variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disease-states; and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about
20 0.14 mg to about 14.3 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.7 mg to about 10 mg/kg of body weight per day; and most preferably, from about 1.4 mg to about 7.2 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 10 mg to about 1.0 gram per day of a
25 compound of the invention, or a pharmaceutically acceptable salt thereof, preferably from about 50 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day.

Preferred Embodiments

Of the compounds of the invention as set forth above in the Summary of the
30 Invention, several groups of compounds are preferred.

A preferred group of compounds is that group wherein the compound is selected from formula (I):



as a single stereoisomer or a mixture thereof; or as a pharmaceutically acceptable salt thereof.

- A preferred subgroup of this group is that subgroup of compounds wherein A is
- 5 -N=; Z¹ and Z² are independently -O-, -OCH₂- or -S(O)_n (where n is 0 to 2); R¹ and R⁴ are each independently hydrogen, halo or -OR¹²; R² is -C(NH)NH₂, -C(NH)N(H)S(O)₂R¹⁵, or -C(NH)N(H)C(O)R¹²; R³ is ureido, guanidino, -OR¹², -C(NH)NH₂, -C(O)N(R¹²)R¹³, -N(R¹²)R¹³, -N(R¹²)C(O)R¹², (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolyl (optionally
- 10 substituted by alkyl); R⁵ and R⁶ are independently hydrogen, halo, alkyl, or haloalkyl; R⁷ is -S(O)_n-(C(R⁹)(R¹⁰))_m-R¹¹ (where n is 0 to 2 and m is 1 to 4); each R⁹ is independently hydrogen, alkyl, -C(O)OR¹², -R¹⁴-C(O)OR¹², -R¹⁴-C(O)N(R¹²)R¹³, -N(R¹²)R¹³, or -R¹⁴-N(R¹²)R¹³; or each R⁹ is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, -OR¹²,
- 15 -SR¹², -N(R¹²)R¹³, -C(O)OR¹², -C(O)N(R¹²)R¹³, -S(O)₂OR¹² and -OP(O)(OR¹²)₂); or each R⁹ is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, -OR¹², -SR¹², -N(R¹²)R¹³, -C(O)OR¹², -C(O)N(R¹²)R¹³, -S(O)₂OR¹² and -OP(O)(OR¹²)₂); each R¹⁰ is independently hydrogen or alkyl; R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³; each R¹² and R¹³ is
- 20 independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl,
- 25 monoalkylaminocarbonyl, or dialkylaminocarbonyl); R¹⁴ is an alkylene or alkylidene chain; and R¹⁵ is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino,
- 30 monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl,

monoalkylaminocarbonyl, or dialkylaminocarbonyl).

A preferred class of this subgroup is that class of compounds wherein A is -N=; Z¹ and Z² are each -O-; R¹ is hydrogen or -OR¹²; R² is -C(NH)NH₂; R³ is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R⁴ is hydrogen; R⁵ and R⁶ are each halo; R⁷ is -S(O)_n-(C(R⁹)(R¹⁰))_m-R¹¹ (where n is 0 to 2 and m is 1 to 4); each R⁹ is independently hydrogen, alkyl, aryl, -C(O)OR¹², -R¹⁴-C(O)OR¹², -R¹⁴-C(O)N(R¹²)R¹³, -N(R¹²)R¹³, or -R¹⁴-N(R¹²)R¹³; each R¹⁰ is independently hydrogen or alkyl; R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³; each R¹² and R¹³ is independently hydrogen or alkyl; R¹⁴ is an alkylene or alkylidene chain; and R¹⁵ is alkyl or aryl.

A preferred subclass of this class is that subclass of compounds wherein A is -N=; Z¹ and Z² are each -O-; R¹ is hydroxy; R² is -C(NH)NH₂; R³ is 1-methylimidazol-2-yl or 1-methylimidazolin-2-yl; R⁴ is hydrogen; R⁵ and R⁶ are each fluoro; R⁷ is -S(O)_n-(C(R⁹)(R¹⁰))_m-R¹¹ (where n is 0 and m is 1 to 4); each R⁹ is independently hydrogen, alkyl, aryl, -C(O)OR¹², -R¹⁴-C(O)OR¹², -N(R¹²)R¹³, or -R¹⁴-N(R¹²)R¹³; each R¹⁰ is independently hydrogen or alkyl; R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³; each R¹² and R¹³ is independently hydrogen or alkyl; R¹⁴ is an alkylene or alkylidene chain; and R¹⁵ is alkyl or aryl.

Of this subclass of compounds, the more preferred compounds are those selected from the group consisting of:

4-hydroxy-3-[(4-(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-methoxycarbonylethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-methoxycarbonylprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(ethoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-

- 3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(3-ethoxycarbonyl-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 5 4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(3-carboxyprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 10 4-hydroxy-3-[(4-(1,2-dicarboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(1-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(2-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 15 4-hydroxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 20 4-hydroxy-3-[(4-(2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and
- 4-hydroxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

Of these compounds, the most preferred compound is 4-hydroxy-3-[(4-(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

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Another preferred subgroup of the above-identified group is that subgroup of compounds wherein A is -N=; Z¹ and Z² are independently -O-, -OCH₂- or -S(O)_n (where n is 0 to 2); R¹ and R⁴ are each independently hydrogen, halo, alkyl, or -OR¹²; R² is -C(NH)NH₂, -C(NH)N(H)C(O)R¹², or -C(NH)N(H)S(O)₂R¹⁵; R³ is ureido, guanidino, -OR¹², -C(NH)NH₂, -C(O)N(R¹²)R¹³, -N(R¹²)R¹³, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R⁵ and R⁶ are independently hydrogen, halo, alkyl, or haloalkyl; R⁷ is -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ (where n is 0 to 2 and

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p is 0 to 4); R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$; each R^{12} and R^{13} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by
 5 halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino,
 10 monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and R^{16} is a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$.

A preferred class of this subgroup is that class of compounds wherein A is $-N=$;
 20 Z^1 and Z^2 are both $-O-$; R^1 is hydrogen or $-OR^{12}$; R^2 is $-C(NH)NH_2$; R^3 is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^4 is hydrogen; R^5 and R^6 are each halo; R^7 is $-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 to 2 and p is 0); R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$; each R^{12} and R^{13} is independently
 25 hydrogen, alkyl, or aralkyl; R^{16} is a carbocyclic ring system selected from the group consisting of cyclopentyl, cyclohexyl, cyclobutyl, and phenyl, and wherein the ring system is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 2 and R^{11} is defined above), and is optionally substituted by halo, or $-C(O)N(R^{12})R^{13}$.

A preferred subclass of this class is that subclass of compounds wherein R^1 is
 30 hydrogen, hydroxy or benzyloxy; R^3 is 1-methylimidazolin-2-yl; and R^5 and R^6 are both fluoro.

Of this subclass the more preferred compounds are selected from the group consisting of:

4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-

3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-aminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-dimethylaminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-(2-carboxyethyl)phenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-(2-ethoxycarbonyl)ethyl)phenyl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine; and
 4-hydroxy-3-[(4-(4-ethoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine.

Of these compounds, the most preferred compound is 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

Another preferred subgroup of the group of compounds described above is that subgroup of compounds wherein A is -N=; Z¹ and Z² are each -O-, -S or -OCH₂; R¹ and R⁴ are independently hydrogen, halo, alkyl or -OR¹²; R² is -C(NH)NH₂, -C(NH)N(H)C(O)R¹², or -C(NH)N(H)S(O)₂R¹⁵; R³ is ureido, guanidino, -OR¹², -C(NH)NH₂, -C(O)N(R¹²)R¹³, -N(R¹²)R¹³, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolynyl (optionally substituted by alkyl); R⁵ and R⁶ are independently hydrogen, halo, alkyl, or haloalkyl; R⁷ is -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ (where n is 0 to 2 and p is 0 to 4); R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³; each R¹² and R¹³ is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by

halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and R^{16} is a mono-, bi- or tricyclic heterocyclic ring system containing from 3 to 15 ring members including carbon and 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur atoms, wherein the carbon, nitrogen and sulfur atoms may be optionally oxidized and wherein the heterocyclic ring system may be partially or fully saturated or aromatic and is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$.

A preferred class of this subgroup is that class of compounds wherein A is $-N=$; Z^1 and Z^2 are each $-O$; R^1 is hydrogen or $-OR^{12}$; R^2 is $-C(NH)NH_2$; R^3 is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^5 and R^6 are each halo; R^7 is $-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 to 2 and p is 0 to 4); R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$; each R^{12} and R^{13} is independently hydrogen, alkyl, or aralkyl; R^{16} is a heterocyclic ring system selected from the group consisting of pyridinyl, imidazolyl, triazinyl, tetrazolyl, and pyrimidinyl, and wherein the heterocyclic ring system is optionally substituted by hydroxy, $-N(R^{12})R^{13}$, or $-C(O)OR^{12}$.

A preferred subclass of this class is that subclass of compounds wherein R^1 is hydrogen, hydroxy or benzyloxy; R^3 is 1-methylimidazolin-2-yl; and R^5 and R^6 are both fluoro.

Of this subclass of compounds, the more preferred compounds are selected from the group consisting of:

- 4-hydroxy-3-[(4-(5-carboxypyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(5-ethoxycarbonylpyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
- 4-hydroxy-3-[(4-(1-methyl-5-carboximidazol-2-yl)thio-6-(3-(1-methyl)imidazolin-

- 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)thio-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)thio-6-(3-(1-methyl)imidazolin-
 5 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)thio-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 10 4-hydroxy-3-[(4-(5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 15 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and
 4-hydroxy-3-[(4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)thio-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.
 20 The most preferred compounds of the invention are the following:
 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 25 4-hydroxy-3-[(4-(2-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine; and
 4-hydroxy-3-[(4-(2-carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine.

Preparation of Compounds of The Invention

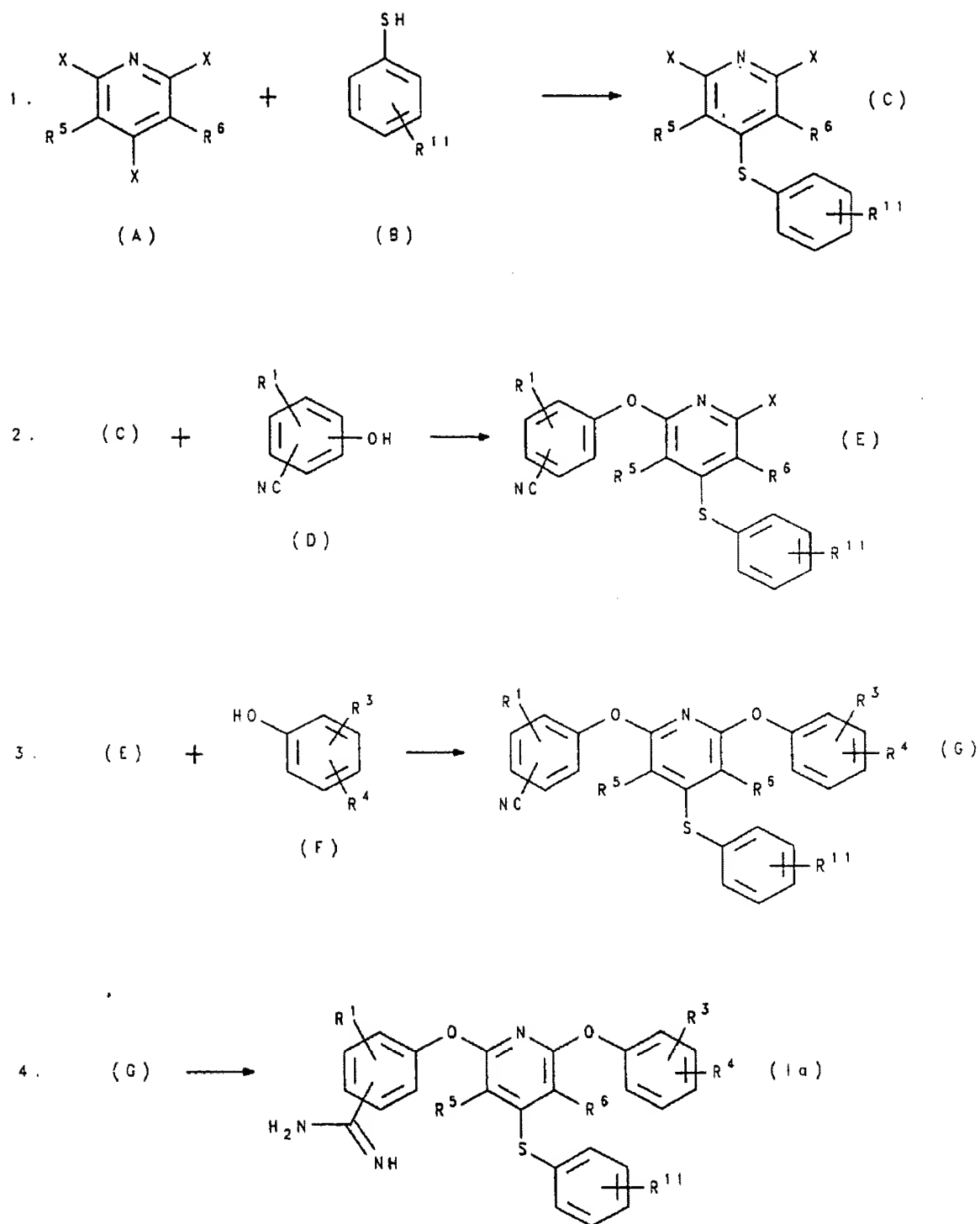
- 30 As a matter of convenience, the following description of the preparation of the compounds of the invention is directed to the preparation of compounds of formula (I) where A is -N=, Z¹ and Z² are both -O-, R² is -C(NH)NH₂, and R⁷ is -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ where n and p are both 0, and R¹⁶ is phenyl substituted by R¹¹,

where R^{11} is as defined above in the Summary of the Invention. It is understood, however, that similar synthetic processes may be used to prepare other compounds of formula (I), (II), (III), (IV), (V), (VI), and (VII). It is also understood that in the following description, combinations of substituents and/or variables (*e.g.*, R^{12} and R^{13}) on the depicted formulae are permissible only if such combinations result in stable compounds.

A. Preparation of Compounds of Formula (Ia)

Compounds of formula (Ia) are compounds of formula (I) where A is $-N=$, Z^1 and Z^2 are both $-O-$, R^2 is $-C(NH)NH_2$, and R^7 is $-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ where n and p are both 0, and R^{16} is phenyl substituted by R^{11} , where R^{11} is as defined above in the Summary of the Invention, and may be prepared as illustrated below in the Reaction Scheme, where each X is independently halo; and R^1 , R^3 , R^4 , R^5 , R^6 and R^{11} are as described above in the Summary of the Invention:

REACTION SCHEME



The mercapto compounds of formula (B) are commercially available, for example from Aldrich Chemical Co., Sigma Chemical Co., or ICN Biomedicals, Inc, or may be prepared according to methods known to those skilled in the art. In addition, other sulfur compounds of the formula $\text{HS(O)}_n\text{-(C(R}^9\text{)(R}^{10}\text{))}_m\text{-R}^{11}$ (where n is 0 and m is 1 to 4) or the formula $\text{HS(O)}_n\text{-(C(R}^{12}\text{)(R}^{13}\text{))}_p\text{-R}^{16}$ (where n is 0 and p is 0 to 4) where each R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are defined above in the Summary of the Invention, are also commercially available, for example, from Aldrich Chemical Co., Maybridge Co., and Jannsen Co., or may be prepared according to methods known to those skilled in the art, and may be similarly used in the above Reaction Scheme in place of the compound of formula (B) to produce the corresponding compounds invention where R^7 is $\text{-S(O)}_n\text{-(C(R}^9\text{)(R}^{10}\text{))}_m\text{-R}^{11}$ (where n is 0 and m is 1 to 4) or $\text{-S(O)}_n\text{-(C(R}^{12}\text{)(R}^{13}\text{))}_p\text{-R}^{16}$ (where n is 0 and p is 0 to 4) where each R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{16} are defined above in the Summary of the Invention. The compounds of formula (A), (D), and (F) are commercially available, for example, from Aldrich Chemical Co., or may be prepared according to methods known to those skilled in the art.

In general, the compounds of formula (Ia) are prepared by first treating a compound of formula (A) with a compound of formula (B) in an aprotic solvent, for example, DMSO, in the presence of a base, for example, triethylamine, at -20°C to 50°C , preferably at ambient temperature, for about 20 to 40 hours. The compound of formula (C) is then isolated from the reaction mixture by standard techniques, such as extraction, filtration and *in vacuo* removal of solvent.

The resulting compound of formula (C) in an aprotic solvent, for example, acetonitrile, is treated with an equimolar amount of a compound of formula (D) in the presence of a base, for example, cesium carbonate, at temperatures between about 20°C and 120°C , preferably at ambient temperature, for a period of time sufficient to complete the desired reaction as monitored by thin layer chromatography (TLC). The compound of formula (E) is then isolated from the reaction mixture by standard isolation techniques, such as extraction, *in vacuo* removal of solvent, and flash chromatography.

The compound of formula (E) in an aprotic solvent, for example, DMSO, is then treated with an equimolar amount of a compound of formula (F) in the presence of a base, for example, cesium carbonate, at temperatures between about 20°C and 120°C , preferably at about 35°C , for a period of time sufficient to complete the desired reaction, for example, for about 13 hours. The reaction mixture is cooled to ambient temperature and the compound of formula (G) is then isolated from the reaction mixture

through standard isolated techniques, such as extraction, *in vacuo* removal of solvent, and flash chromatography.

The compound of formula (G) is dissolved in an anhydrous alkanol, preferably ethanol, and then anhydrous mineral acid, preferably HCl, is added to the solution over
5 a period of time sufficient to incorporate the acid into the solution while maintaining the reaction temperatures at about -78°C. After incorporation is complete, the reaction vessel is sealed and the reaction mixture is allowed to warm to ambient temperature and stirred between 12 and 24 hours, preferably for about 16 hours. The solvent is removed *in vacuo* and the resulting residue is dissolved in fresh anhydrous alkanol,
10 preferably ethanol, and then treated with anhydrous ammonia (gas) at temperatures from between ambient temperature and about 100°C from about 1 to about 48 hours, preferably at about 60°C and for about 2 hours. The compound of formula (Ia) is then isolated from the reaction mixture by standard isolation techniques, for example, *in vacuo* removal of solvent and purification by high performance liquid chromatography
15 (HPLC).

Alternatively, instead of treating the resulting residue above with anhydrous ammonia (gas), the resulting residue may be treated with a compound of the formula $\text{NH}_2\text{OR}^{12}$ to afford the corresponding compound of formula (Ia) wherein R^2 is $-\text{C}(\text{NH})\text{N}(\text{H})\text{OR}^{12}$.

20 In addition, compounds of formula (Ia) may be treated under standard transesterification conditions with an alcohol of the formula R^{12}OH where R^{12} is aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) to produce compounds of the
25 invention where R^{12} is optionally substituted aryl.

Compounds of formula (Ia) wherein R^3 is $-\text{C}(\text{NH})\text{NH}_2$ or $-\text{C}(\text{NH})\text{N}(\text{H})\text{OR}^{12}$ are produced from the corresponding cyano compounds in a similar manner as that described above for compound of formula (G).

30 In addition, compounds of formula (Ia) wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{11} , or R^{16} contains a $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$ group or a $-\text{C}(\text{O})\text{OR}^{12}$ group (where each R^{12} or R^{13} is independently alkyl, optionally substituted aryl or optionally substituted aralkyl) may be hydrolyzed under acidic conditions to prepare corresponding compounds of the invention where R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{11} , or R^{16} contains a $-\text{C}(\text{O})\text{OH}$ group.

In addition, compounds of formula (Ia) wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{11} or R^{16}

contains a $-C(O)OR^9$ group where R^9 is hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl may be amidated under standard amidation conditions to form the corresponding compounds of formula (Ia) where R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{11} , or R^{16} contains a $-C(O)N(R^9)R^{10}$ group where R^9 and R^{10} are independently hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl.

In addition, compounds of formula (Ia) where R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{12} , R^{13} or R^{15} contains a nitro group may be reduced under standard conditions to produce the corresponding compounds of formula (Ia) where R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{12} , R^{13} or R^{15} contains an amino group, which can be treated with the appropriate alkylating agents or acylating agents to afford the corresponding compounds of formula (Ia) where R^1 , R^3 , R^4 , R^5 , R^6 , R^9 , R^{12} , R^{13} or R^{15} contains $-N(R^{12})R^{13}$ or $-N(R^{12})C(O)R^{13}$ where each R^{12} and R^{13} is independently hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl.

Compounds of formula (Ia) may be further treated with the appropriate acid halide, preferably acid chloride, or with the appropriate acid anhydride or an equivalent, to yield compounds of the invention wherein R^2 is $-C(NH)N(H)C(O)R^{12}$ where R^{12} is hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl.

Alternatively, compounds of formula (Ia) may further be treated with carbamoyl chlorides or their equivalents to yield compounds of the invention where R^2 is

$-C(NH)N(H)C(O)OR^{12}$ where R^{12} is described above in the Summary of the Invention.

Alternatively, compounds of formula (Ia) may be further treated with compounds of the formula $R^{15}-S(O)_2$ -imidazole (where R^{15} is described in the Summary of the Invention) in a polar solvent, such as methylene chloride, at ambient temperature to afford compounds of the invention where R^2 is $-C(NH)N(H)S(O)_2R^{15}$.

Alternatively, compounds of formula (Ia) may be further treated with an appropriately N - R^{12} -substituted phenylcarbamate in a polar solvent, preferably methylene chloride, at ambient temperature, for about 6 to 24 hours, preferably for about 12 hours, to afford compounds of the invention where R^2 is $-C(NH)N(H)C(O)N(H)R^{12}$.

In addition, compounds of the formula $HS(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 and m is 1 to 4) or the formula $HS(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 and p is 0 to 4) where each R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are defined above in the Summary of the Invention which may be used in place of the compound of formula (B) above and which contain additional reactive hydroxy or amino groups may be treated with the appropriate

oxygen- or nitrogen-protecting group prior to Step 1 and then deprotected as desired to provide the free hydroxy or amino groups.

In addition, compounds of formula (Ia) which contain an unoxidized sulfur atom may be oxidized with the appropriate oxidizing agent to produce compounds containing
5 oxidized sulfur (-S(O)_q- where q is 1 or 2).

* * * * *

The following specific preparations and examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

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PREPARATION 1

Compounds of formula (C)

A. To a solution of methyl thiosalicylate (1.0 g, 5.9 mmol) in dry DMF (15 mL) at 0°C was added pentafluoropyridine (1.2 g, 7.1 mmol) and cesium carbonate (2.5 g, 7.7 mmol). The resultant mixture was stirred at ambient temperature for 5
15 hours then poured into 100 mL of 0.5 M aqueous KOH solution and 100 mL of ethyl acetate. The aqueous layer was separated and extracted with another 100 mL of ethyl acetate. The combined organic extracts were washed with 0.5 M aqueous KOH solution (100 mL) then brine (100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to afford 1.8 g (98% yield) of 4-(2-methoxycarbonylphenyl)thio-2,3,5,6-
20 tetrafluoropyridine as a crystalline solid, NMR (CDCl₃) 8.1 (dd, 1), 7.4 (m, 1), 7.4 (tt, 1), 7.0 (d, 1), 4.0 (s, 3) ppm.

B. In a similar manner, the following compounds of formula (C) are made:
4-(2-carboxyphenyl)thio-2,3,5,6-tetrafluoropyridine;
4-(carboxymethyl)thio-2,3,5,6-tetrafluoropyridine;
25 4-(2-methoxycarbonyl)thio-2,3,5,6-tetrafluoropyridine;
4-(3-methoxycarbonylprop-1-yl)thio-2,3,5,6-tetrafluoropyridine;
4-(ethoxycarbonylmethyl)thio-2,3,5,6-tetrafluoropyridine;
4-(3-carboxy-3-aminoprop-1-yl)thio-2,3,5,6-tetrafluoropyridine;
4-(1-carboxy-2-aminoethyl)thio-2,3,5,6-tetrafluoropyridine;
30 4-(1-ethoxycarbonyl-2-aminoethyl)thio-2,3,5,6-tetrafluoropyridine;
4-(3-ethoxycarbonyl-3-aminoprop-1-yl)thio-2,3,5,6-tetrafluoropyridine;
4-(3-carboxy-3-aminoprop-1-yl)thio-2,3,5,6-tetrafluoropyridine;
4-(3-carboxyprop-1-yl)thio-2,3,5,6-tetrafluoropyridine;

- 4-(1,2-dicarboxyethyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(1-carboxyethyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(2-carboxyethyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(1,1-diphenyl-1-carboxymethyl)thio-2,3,5,6-tetrafluoropyridine;
 5 4-(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(2-carboxy-2-aminoethyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(2-ethoxycarbonyl-2-aminoethyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(2-aminocarbonyl-3-chlorophenyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(2-dimethylaminocarbonyl-3-chlorophenyl)thio-2,3,5,6-tetrafluoropyridine;
 10 4-(2-aminocarbonylphenyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(2-dimethylaminocarbonylphenyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(4-(2-carboxyethyl)phenyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(4-(2-ethoxycarbonyl)phenyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(4-carboxyphenyl)thio-2,3,5,6-tetrafluoropyridine;
 15 4-(4-ethoxycarbonylphenyl)thio-2,3,5,6-tetrafluoropyridine;
 4-(5-carboxypyridin-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(5-ethoxycarbonylpyridin-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(1-methyl-5-carboxyimidazol-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(1-methyl-5-methoxycarbonylimidazol-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 20 4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(5-carboxypyrimidin-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(5-ethoxycarbonylpyrimidin-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(4-amino-5-carboxypyrimidin-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 25 4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)thio-2,3,5,6-tetrafluoropyridine;
 4-(4-hydroxy-5-carboxypyrimidin-2-yl)thio-2,3,5,6-tetrafluoropyridine; and
 4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)thio-2,3,5,6-tetrafluoropyridine.

PREPARATION 2

Compounds of formula (E)

- 30 A. To a solution of 4-(2-methoxycarbonylphenyl)thio-2,3,5,6-tetrafluoropyridine (1.8 g, 5.7 mmol) in DMF (25 mL) was added 2-benzyloxy-5-cyanophenol (1.3 g, 5.8 mmol) and cesium carbonate (2.2 g, 6.8 mmol). The resultant mixture was stirred at 40°C for 12 hours. The mixture was then cooled to ambient

temperature and poured into 100 mL of 0.5 M aqueous KOH solution and 100 mL of ethyl acetate. The aqueous layer was separated and extracted twice further with 100 mL portions of ethyl acetate. The combined organic extracts were washed with 0.5 M aqueous KOH solution (200 mL), then brine (200 mL), dried over MgSO_4 ,
 5 filtered, and concentrated *in vacuo* to afford a yellow solid. Recrystallization from ethyl acetate/hexanes afforded 2.4 g (82% yield) of 4-benzyloxy-3-[(4-(2-methoxycarbonylphenyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile, a compound of formula (E), as a white, crystalline solid: NMR (CDCl_3) 8.0 (m, 1), 7.5 (m, 2), 7.4-7.1 (m, 8), 6.8 (br t, 1), 5.2 (s, 2), 4.0 (s, 3) ppm.

- 10 B. In a similar manner, the following compounds of formula (E) are made:
 4-benzyloxy-3-[(4-(2-carboxyphenyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(carboxymethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(2-methoxycarbonyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 15 4-benzyloxy-3-[(4-(3-methoxycarbonylprop-1-yl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(ethoxycarbonylmethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 20 4-benzyloxy-3-[(4-(1-carboxy-2-aminoethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(3-ethoxycarbonyl-3-aminoprop-1-yl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 25 4-benzyloxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(3-carboxyprop-1-yl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(1,2-dicarboxyethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 30 4-benzyloxy-3-[(4-(1-carboxyethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(2-carboxyethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
 4-benzyloxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-3,5,6-trifluoropyridin-

- 2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(2-carboxy-2-aminoethyl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)thio-3,5,6-trifluoropyridin-
5 2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
10 4-benzyloxy-3-[(4-(2-aminocarbonylphenyl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(2-dimethylaminocarbonylphenyl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(4-(2-carboxyethyl)phenyl)thio-3,5,6-trifluoropyridin-
15 2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(4-(2-ethoxycarbonylethyl)phenyl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(4-carboxyphenyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(4-ethoxycarbonylphenyl)thio-3,5,6-trifluoropyridin-
20 2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(5-carboxypyridin-2-yl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(5-ethoxycarbonylpyridin-2-yl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(1-methyl-5-carboxyimidazol-2-yl)thio-3,5,6-trifluoropyridin-
25 2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
30 4-benzyloxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)thio-
3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(5-carboxypyrimidin-2-yl)thio-3,5,6-trifluoropyridin-
2-yl)oxy]benzonitrile;
4-benzyloxy-3-[(4-(5-ethoxycarbonylpyrimidin-2-yl)thio-3,5,6-trifluoropyridin-

2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)thio-3,5,6-trifluoropyridin-

2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)thio-3,5,6-trifluoropyridin-

5 2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)thio-3,5,6-trifluoropyridin-

2-yl)oxy]benzonitrile; and

4-benzyloxy-3-[(4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)thio-3,5,6-trifluoropyridin-

2-yl)oxy]benzonitrile.

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PREPARATION 3

Compounds of formula (E)

A. To a solution of pentafluoropyridine (1.9 g, 11.2 mmol) in acetonitrile (25 mL) at 0°C was added methyl thioglycolate (1.0 mL, 11.2 mmol) and cesium carbonate (4.4 g, 13.5 mmol). The resultant mixture was allowed to warm slowly to ambient temperature and stirred for 16 hours. To the mixture was added 2-benzyloxy-5-cyanophenol (2.6 g, 11.5 mmol) and cesium carbonate (4.4 g, 13.5 mmol). The resultant mixture was stirred at 40°C for 16 hours. The mixture was then cooled to ambient temperature and poured into 150 mL of 0.5 M aqueous KOH solution and 150 mL of ethyl acetate. The organic layer was separated and washed further with 150 mL of 0.5 M aqueous KOH solution, then brine (150 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography on silica gel afforded 2.9 g (56% yield) of 4-benzyloxy-3-[(4-(methoxycarbonylmethyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile, a compound of formula (E), as a pale yellow oil: NMR (CDCl₃) 7.5-7.0 (m, 8), 5.1 (s, 2), 3.8 (s, 2), 3.7 (s, 3) ppm.

25

PREPARATION 4

Compounds of formula (G)

A. To a solution of 4-benzyloxy-3-[(4-(2-methoxycarbonylphenyl)thio-3,5,6-trifluoropyridin-2-yl)oxy]benzonitrile (2.0 g, 3.8 mmol) in DMSO (30 mL) was added 3-((1-methyl)imidazolin-2-yl)phenol (0.68 g, 3.9 mmol) and cesium carbonate (1.4 g, 4.3 mmol). The resultant mixture was stirred at 35°C for 12 hours, then 45°C for 4 hours. The mixture was then cooled to ambient temperature and poured into 150 mL of

30

0.5 M aqueous KOH solution and 150 mL of ethyl acetate. The aqueous layer was separated and extracted with another 150 mL of ethyl acetate. The combined organic extracts were washed with 0.5 M aqueous KOH solution (200 mL) then brine (200 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash

5 chromatography on silica gel afforded 2.2 g (85% yield) of 4-benzyloxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile, a compound of formula (G), as a solid foam; NMR (CDCl_3) 8.1 (br d, 1), 7.4-6.9 (m, 15), 5.0 (s, 2), 4.0 (s, 3), 3.9 (t, 2), 3.5 (t, 2), 2.7 (s, 3) ppm.

B. In a similar manner, the following compound of formula (G) was made:

10 4-benzyloxy-3-[(4-(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile.

C. In a similar manner, the following compounds are made:

4-benzyloxy-3-[(4-(2-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

15 4-benzyloxy-3-[(4-(carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(2-methoxycarbonyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

20 4-benzyloxy-3-[(4-(3-methoxycarbonylprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(ethoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

25 4-benzyloxy-3-[(4-(1-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

30 4-benzyloxy-3-[(4-(3-ethoxycarbonyl-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(3-carboxyprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

- 4-benzyloxy-3-[(4-(1,2-dicarboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(1-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 5 4-benzyloxy-3-[(4-(2-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 10 4-benzyloxy-3-[(4-(2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 15 4-benzyloxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(2-aminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 20 4-benzyloxy-3-[(4-(2-dimethylaminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(4-(2-carboxyethyl)phenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 25 4-benzyloxy-3-[(4-(4-(2-ethoxycarbonyl)phenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(4-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(4-ethoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 30 4-benzyloxy-3-[(4-(5-carboxypyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;
- 4-benzyloxy-3-[(4-(5-ethoxycarbonylpyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(1-methyl-5-carboxyimidazol-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)thio-

6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

5 4-benzyloxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)thio-

6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-

10 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-

2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-

2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

15 4-benzyloxy-3-[(4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)thio-

6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile;

4-benzyloxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-

2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile; and

4-benzyloxy-3-[(4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)thio-

20 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile.

EXAMPLE 1

Compounds of formula (I)

A. A solution of 4-benzyloxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzonitrile (0.85 g,
25 1.3 mmol) in absolute ethanol (25 mL) was cooled to -78°C and HCl(g) was bubbled through the mixture for 15 minutes. The reaction vessel was sealed and the resultant mixture was stirred at ambient temperature for 15 hours, then concentrated of all volatiles *in vacuo* without heating to afford a solid white foam. This foam was dissolved in absolute ethanol (20 mL) and cooled to -78°C and NH₃(g) was bubbled
30 through the mixture for 5 minutes. The reaction vessel was sealed and the resultant mixture was stirred at 55°C. After 2.5 hours, the mixture was cooled to ambient temperature and concentrated *in vacuo*. Purification by HPLC on a C18 Dynamax column with 30-40% acetonitrile in water gradient with 0.1% trifluoroacetic acid

afforded 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt, a compound of formula (I), as a white solid: NMR (DMSO- d_6)/TFA) 10.3 (s, 1), 9.0 (br s, 2), 8.8 (br s, 2), 8.0 (dd, 1), 7.7-7.3 (m, 8), 7.2 (d, 1), 7.0 (d, 1), 4.1-3.8 (m, 4), 3.9 (m, 3), 2.9 (s, 3) ppm.

B. In a similar manner, the following compound of formula (I) was made: 4-hydroxy-3-[(4-(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt, as a white solid: NMR (DMSO- d_6)/TFA) 10.2 (s, 1), 9.0 (br s, 2), 8.8 (br s, 2), 7.6-7.3 (m, 6), 7.0 (d, 1), 4.1 (br s, 2), 4.1 (q, 2), 4.1-3.8 (m, 4), 3.0 (s, 3), 1.2 (t, 3) ppm.

C. In a similar manner, the following compounds of formula (I) are made: 4-hydroxy-3-[(4-(2-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(2-methoxycarbonylpropyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(3-methoxycarbonylpropyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(ethoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(3-carboxy-3-aminopropyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(1-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(3-ethoxycarbonyl-3-aminopropyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(3-carboxy-3-aminopropyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(3-carboxypropyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidinium trifluoroacetate salt;

4-hydroxy-3-[(4-(1,2-dicarboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-

- 3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
5 3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
10 4-hydroxy-3-[(4-(2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-
15 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-aminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
20 4-hydroxy-3-[(4-(2-dimethylaminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-(2-carboxyethyl)phenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-(2-ethoxycarbonyl)phenyl)thio-6-(3-(1-methyl)imidazolin-
25 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-ethoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
30 4-hydroxy-3-[(4-(5-carboxypyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-ethoxycarbonylpyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-methyl-5-carboxyimidazol-2-yl)thio-6-(3-(1-methyl)imidazolin-

2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)thio-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)thio-6-(3-(1-methyl)imidazolin-
 5 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)thio-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 10 4-hydroxy-3-[(4-(5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 15 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and
 4-hydroxy-3-[(4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)thio-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

20 D. The compounds prepared above are oxidized with the appropriate oxidizing agent to the following compounds:

4-hydroxy-3-[(4-(methoxycarbonylmethyl)sulfinyl-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)sulfinyl-6-(3-(1-methyl)imidazolin-
 25 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(2-carboxyphenyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(carboxymethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;
 30 4-hydroxy-3-[(4-(2-methoxycarbonyl-ethyl)sulfinyl-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(3-methoxycarbonylprop-1-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(ethoxycarbonylmethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-

- 3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-carboxy-2-aminoethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
5 3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(3-ethoxycarbonyl-3-aminoprop-1-yl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
10 4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(3-carboxyprop-1-yl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,2-dicarboxyethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
15 3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-carboxyethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-carboxyethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
20 4-hydroxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-carboxy-2-aminoethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
25 4-hydroxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
30 4-hydroxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-aminocarbonylphenyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-dimethylaminocarbonylphenyl)sulfinyl-6-(3-(1-methyl)imidazolin-

- 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-(2-carboxyethyl)phenyl)sulfinyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-(2-ethoxycarbonyl)phenyl)sulfinyl-6-(3-(1-methyl)imidazolin-
5 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-carboxyphenyl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-ethoxycarbonyl)phenyl)sulfinyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
10 4-hydroxy-3-[(4-(5-carboxypyridin-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-ethoxycarbonyl)pyridin-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-methyl-5-carboxyimidazol-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
15 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)sulfinyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)sulfinyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
20 4-hydroxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)sulfinyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-carboxypyrimidin-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-ethoxycarbonyl)pyrimidin-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
25 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-amino-5-ethoxycarbonyl)pyrimidin-2-yl)sulfinyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
30 4-hydroxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)sulfinyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-hydroxy-5-ethoxycarbonyl)pyrimidin-2-yl)sulfinyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(methoxycarbonylmethyl)sulfonyl-6-(3-(1-methyl)imidazolin-

- 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-carboxyphenyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
5 3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(carboxymethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(2-methoxycarbonyl-ethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
10 4-hydroxy-3-[(4-(3-methoxycarbonylprop-1-yl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(ethoxycarbonylmethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
15 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-carboxy-2-aminoethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
20 4-hydroxy-3-[(4-(3-ethoxycarbonyl-3-aminoprop-1-yl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
25 4-hydroxy-3-[(4-(3-carboxyprop-1-yl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,2-dicarboxyethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-carboxyethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
30 4-hydroxy-3-[(4-(2-carboxyethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)sulfonyl-

- 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(2-carboxy-2-aminoethyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
5 4-hydroxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)sulfonyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
10 4-hydroxy-3-[(4-(2-aminocarbonylphenyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(2-dimethylaminocarbonylphenyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(4-(2-carboxyethyl)phenyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
15 4-hydroxy-3-[(4-(4-(2-ethoxycarbonyl)ethyl)phenyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(4-carboxyphenyl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy}benzamidine;
20 4-hydroxy-3-[(4-(4-ethoxycarbonylphenyl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(5-carboxypyridin-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(5-ethoxycarbonylpyridin-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
25 4-hydroxy-3-[(4-(1-methyl-5-carboxyimidazol-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-
2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)sulfonyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
30 4-hydroxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)sulfonyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)sulfonyl-
6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy}benzamidine;
4-hydroxy-3-[(4-(5-carboxypyrimidin-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-

2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(5-ethoxycarbonylpyrimidin-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-
 5 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)sulfonyl-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)sulfonyl-6-(3-(1-methyl)imidazolin-
 2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and
 10 4-hydroxy-3-[(4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)sulfonyl-
 6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

EXAMPLE 2

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of the invention, or a
 15 pharmaceutically acceptable salt thereof, *e.g.*, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine:

A.	<u>Ingredients</u>	<u>% wt./wt.</u>
	Compound of the invention	20.0%
20	Lactose	79.5%
	Magnesium stearate	0.5%

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage.

B.	<u>Ingredients</u>	<u>% wt./wt.</u>
25	Compound of the invention	20.0%
	Magnesium stearate	0.9%
	Starch	8.6%
	Lactose	69.6%
	PVP (polyvinylpyrrolidone)	0.9%

30 The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid. The formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tableting machine.

C. Ingredients

	Compound of the invention	0.1 g
	Propylene glycol	20.0 g
	Polyethylene glycol 400	20.0 g
5	Polysorbate 80	1.0 g
	Water	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

10	D. <u>Ingredients</u>	<u>% wt./wt.</u>
	Compound of the invention	20.0%
	Peanut Oil	78.0%
	Span 60	2.0%

The above ingredients are melted, mixed and filled into soft elastic capsules.

15	E. <u>Ingredients</u>	<u>% wt./wt.</u>
	Compound of the invention	1.0%
	Methyl or carboxymethyl cellulose	2.0%
	0.9% saline	q.s. 100 mL

The compound of the invention is dissolved in the cellulose/saline solution, filtered and bottled for use.

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidide:

	<u>Ingredients</u>	
	Compound of the invention	0.02 g
	Propylene glycol	20.0 g
30	Polyethylene glycol 400	20.0 g
	Polysorbate 80	1.0 g
	0.9% Saline solution	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene

glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2 μ membrane filter and packaged under sterile conditions.

EXAMPLE 4

5 This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine:

10	<u>Ingredients</u>	<u>% wt./wt.</u>
	Compound of the invention	1.0%
	Polyethylene glycol 1000	74.5%
	Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into
15 molds containing 2.5 g total weight.

EXAMPLE 5

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine:

20	<u>Ingredients</u>	<u>% wt./wt.</u>
	Micronized compound of the invention	1.0%
	Micronized lactose	99.0%

25 The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump.

EXAMPLE 6

This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of the invention, or a
30 pharmaceutically acceptable salt thereof, *e.g.*, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-

2-yl)oxy]benzamidine:

<u>Ingredients</u>	<u>% wt./wt.</u>
Compound of the invention	0.005%
Water	89.995%
5 Ethanol	10.000%

The compound of the invention is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

EXAMPLE 7

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine:

<u>Ingredients</u>	<u>% wt./wt.</u>
15 Compound of the invention	0.10%
Propellant 11/12	98.90%
Oleic acid	1.00%

The compound of the invention is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

EXAMPLE 8

(*In vitro* assay for Factor Xa and Thrombin)

This assay demonstrates the activity of the compounds of the invention towards factor Xa, thrombin and tissue plasminogen activator. The activities were determined as an initial rate of cleavage of the peptide *p*-nitroanilide by the enzyme. The cleavage product, *p*-nitroaniline, absorbs at 405 nm with a molar extinction coefficient of 9920 M⁻¹cm⁻¹.

Reagents and Solutions:

Dimethyl sulfoxide (DMSO) (Baker analyzed grade).

30 Assay buffer:

50 mM TrisHCl, 150 mM NaCl, 2.5 mM CaCl₂, and
0.1% polyethylene glycol 6000, pH 7.5.

Enzymes (Enzyme Research Lab.):

1. Human factor Xa stock solution: 0.281 mg/mL in assay buffer, stored at -80°C (working solution (2X): 106 ng/mL or 2 nM in assay buffer, prepare prior to use).
2. Human thrombin stock solution: Stored at -80°C (working solution (2X): 1200 ng/mL or 40 nM in assay buffer, prepare prior to use).
3. Human tissue plasminogen activator (tPA) (Two chains, Sigma) stock solution: 1 mg/mL, stored at -80°C (working solution (2X): 1361 ng/mL in assay buffer, prepare prior to use).

Chromogenic substrates (Pharmacia Hepar Inc.):

1. S2222 (FXa assay) stock solution: 6 mM in deionized H_2O , store at 4°C (working solution (4X): 656 μM in assay buffer).
2. S2302 (Thrombin assay) stock solution: 10 mM in deionized H_2O , stored at 4°C (working solution (4X): 1200 μM in assay buffer).
3. S2288 (tPA assay) stock solution: 10 mM in deionized H_2O , stored at 4°C (working solution (4X): 1484 μM in assay buffer).

Standard inhibitor compound stock solution:

5 mM in DMSO, stored at -20°C .

Test compounds (compounds of the invention) stock solutions:

10 mM in DMSO, stored at -20°C .

Assay procedure:

Assays were performed in 96-well microtiter plates in a total volume of 200 μl . Assay components were in final concentration of 50 mM TrisHCl, 150 mM NaCl, 2.5 mM CaCl_2 , 0.1% polyethylene glycol 6000, pH 7.5, in the absence or presence of the standard inhibitor or the test compounds and enzyme and substrate at following concentrations: (1) 1 nM factor Xa and 164 μM S2222; (2) 20 nM thrombin and 300 μM S2302; and (3) 10 nM tPA and 371 μM S2288. Concentrations of the standard inhibitor compound in the assay were from 5 μM to 0.021 μM in 1 to 3 dilution. Concentration of the test compounds in the assay typically were from 10 μM to 0.041 μM in 1 to 3 dilution. For potent test compounds, the concentrations used in the factor Xa assay were further diluted 100 fold (100 nM to 0.41 nM) or 1000 fold (10 nM to 0.041 nM). All substrate concentrations used are equal to their K_m values under the present assay conditions. Assays were performed at ambient temperature.

The first step in the assay was the preparation of 10 mM test compound stock solutions in DMSO (for potent test compounds, 10 mM stock solutions were further

diluted to 0.1 or 0.01 mM for the factor Xa assay), followed by the preparation of test compound working solutions (4X) by a serial dilutions of 10 mM stock solutions with Biomek 1000 (or Multiprobe 204) in 96 deep well plates as follows:

- 5 (a) Prepare a 40 μ M working solution by diluting the 10 mM stock 1 to 250 in assay buffer in 2 steps: 1 to 100, and 1 to 2.5.
- (b) Make another five serial dilutions (1:3) of the 40 μ M solution (600 μ L for each concentration). A total of six diluted test compound solutions were used in the assay.

10 Standard inhibitor compound (5 mM stock) or DMSO (control) went through the same dilution steps as those described above for test compounds.

The next step in the assay was to dispense 50 μ L of the test compound working solutions (4X) (from 40 μ M to 0.164 μ M) in duplicate to microtiter plates with Biomek or MP204. To this was added 100 μ L of enzyme working solution (2X) with Biomek or MP204. The resulting solutions were incubated at ambient temperature for 10 minutes.

15 To the solutions was added 50 μ L of substrate working solution (4X) with Biomek or MP204.

The enzyme kinetics were measured at 405 nm at 10 seconds intervals for five minutes in a THERMOmax plate reader at ambient temperature.

Calculation of K_i of the Test compounds:

20 Enzyme rates were calculated as mOD/min based on the first two minutes readings. The IC_{50} values were determined by fitting the data to the log-logit equation (linear) or the Morrison equation (non-linear) with an EXCEL spread-sheet. K_i values were then obtained by dividing the IC_{50} by 2. Routinely, K_i (factor Xa) values less than 3 nM were calculated from the Morrison equation.

25 Compounds of the invention, when tested in this assay, demonstrated the selective ability to inhibit human factor Xa and human thrombin.

EXAMPLE 9

(In vitro assay for Human Prothrombinase)

30 This assay demonstrates the ability of the compounds of the invention to inhibit prothrombinase. Prothrombinase (PTase) catalyzes the activation of prothrombin to yield fragment 1.2 plus thrombin with meizothrombin as the intermediate. This assay is an end point assay. Activity of the prothrombinase is measured by activity of thrombin (one of the reaction products) or by the amount of thrombin formed/time based on a

thrombin standard curve (nM vs mOD/min). For determination of IC_{50} (PTase) of the compounds of the invention, PTase activity was expressed by thrombin activity (mOD/min).

Materials:

5 Enzymes:

1. Human factor Va (Haematologic Technologies Inc., Cat# HCVA-0110) working solution: 1.0 mg/mL in 50% glycerol, 2 mM $CaCl_2$, stored at $-20^{\circ}C$.
2. Human factor Xa (Enzyme Res. Lab. cat# HFXa1011) working solution: 0.281 mg/mL in assay buffer (without BSA), stored at $-80^{\circ}C$.
- 10 3. Human prothrombin (FII) (Enzyme Res. Lab., Cat# HP1002) working solution: Diluted FII to 4.85 mg/mL in assay buffer (without BSA), stored at $-80^{\circ}C$.

Phospholipid (PCPS) vesicles:

PCPS vesicles (80%PC, 20%PS) were prepared by modification of the method reported by Barenholz *et al.*, *Biochemistry* (1977), Vol. 16, pp. 2806-2810.

15 Phosphatidyl serine (Avanti Polar Lipids, Inc., Cat#840032):

10 mg/mL in chloroform, purified from brain, stored $-20^{\circ}C$ under nitrogen or argon.

Phosphatidyl Choline (Avanti Polar Lipids, Inc., Cat# 850457):

50 mg/ml in chloroform, synthetic 16:0-18:1 Palmitoyl-Oleoyl, stored at $-20^{\circ}C$ under nitrogen or argon.

20 Spectrozyme-TH (American Diagnostica Inc., Cat# 238L, 50 μ moles, stored at room temperature) working solution: Dissolved 50 μ moles in 10 mL dH_2O .

BSA (Sigma Chem Co., Cat# A-7888, FractionV, RIA grade).

25 Assay buffer: 50 mM TrisHCl, pH 7.5, 150 mM NaCl, 2.5 mM $CaCl_2$, 0.1% PEG 6000 (BDH), 0.05% BSA (Sigma, Fr.V, RIA grade).

For one plate assay, prepare the following working solutions:

1. Prothrombinase complex:

(a) 100 μ M PCPS (27.5 μ L of PCPS stock (4.36 mM) diluted to final 1200 μ L with assay buffer.

30 (b) 25 nM Human factor Va: 5.08 μ L of Va stock (1 mg/mL) was diluted to final 1200 μ L with assay buffer.

(c) 5 pM Human factor Xa: Dilute factor Xa stock (0.281 mg/mL) 1:1,220,000 with assay buffer. Prepare at least 1200 μ L.

Combine equal volumes (1100 μ L) of each component in the order of PCPS, Va

and Xa. Let stand at ambient temperature for 5 to 10 minutes and use immediately or store in ice (bring to ambient temperature before use).

2. 6 μ M Human prothrombin (FII): dilute 124 μ L of FII stock (4.85 mg/mL) to final 1400 μ L with assay buffer.
- 5 3. 20 mM EDTA/Assay buffer: 0.8 mL of 0.5 M EDTA (pH 8.5) plus 19.2 mL assay buffer.
4. 0.2 mM Spectrozyme-TH/EDTA buffer: 0.44 mL of SPTH stock (5 mM) plus 10.56 mL of 20 mM EDTA/assay buffer.
5. Test compounds (compounds of the invention):
- 10 Prepare a working solution (5X) from 10 mM stock (DMSO) and make a series of 1:3 dilution. Compounds were assayed at 6 concentrations in duplicate.

Assay conditions and procedure:

Prothrombinase reaction was performed in final 50 μ L of mixture containing PTase (20 μ M PCPS, 5 nM hFVa, and 1 pM hFXa), 1.2 μ M human factor II and varied
15 concentration of the test compounds (5 μ M to 0.021 μ M or lower concentration range). Reaction was started by addition of PTase and incubated for 6 minutes at room temperature. Reaction was stopped by addition of EDTA/buffer to final 10 mM. Activity of thrombin (product) was then measured in the presence of 0.1 mM of Spectrozyme-TH as substrate at 405 nm for 5 minutes (10 seconds intervals) at
20 ambient temperature in a THEROmax microplate reader. Reactions were performed in 96-well microtiter plates.

In the first step of the assay, 10 μ L of diluted test compound (5X) or buffer was added to the plates in duplicate. Then 10 μ L of prothrombin (hFII) (5X) was added to each well. Next 30 μ L PTase was added to each well, mix for about 30 seconds. The
25 plates were then incubated at ambient temperature for 6 minutes.

In the next step, 50 μ L of 20 mM EDTA (in assay buffer) was added to each well to stop the reaction. The resulting solutions were then mixed for about 10 seconds. Then 100 μ L of 0.2 mM spectrozyme was added to each well. The thrombin reaction rate was then measured at 405 nm for 5 minutes at 10 seconds intervals in a Molecular
30 Devices microplate reader.

Calculations:

Thrombin reaction rate was expressed as mOD/min. using OD readings from the five minute reaction. IC₅₀ values were calculated with the log-logit curve fit program.

The compounds of the invention demonstrated the ability to inhibit

pro-thrombinase when tested in this assay.

EXAMPLE 10

(*In vivo* assay)

The following assay demonstrates the ability of the compounds to act as
5 anti-coagulants.

Male rats (250-330 g) were anesthetized with sodium pentobarbital
(90 mg/kg, i.p.) and prepared for surgery. The left carotid artery was cannulated for
the measurement of blood pressure as well as for taking blood samples to monitor
clotting variables (prothrombin time (PT) and activated partial thromboplastin time
10 (aPTT)). The tail vein was cannulated for the purpose of administering the test
compounds (*i.e.*, the compounds of the invention and standards) and the thromboplastin
infusion. The abdomen was opened *via* a mid-line incision and the abdominal vena cava
was isolated for 2-3 cm distal to the renal vein. All venous branches in this 2-3 cm
segment of the abdominal vena cava were ligated. Following all surgery, the animals
15 were allowed to stabilize prior to beginning the experiment. Test compounds were
administered as an intravenous bolus ($t=0$). Three minutes later ($t=3$), a 5-minute
infusion of thromboplastin was begun. Two minutes into the infusion ($t=5$), the
abdominal vena cava was ligated at both the proximal and distal ends. The vessel was
left in place for 60 minutes, after which it was excised from the animal, slit open, the
20 clot (if any) carefully removed, and weighed. Statistical analysis on the results was
performed using a Wilcoxin-matched-pairs signed rank test.

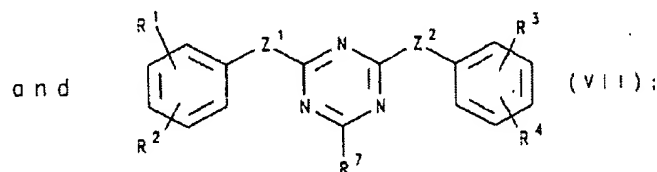
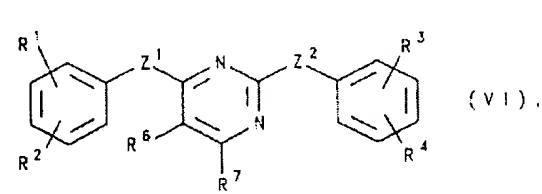
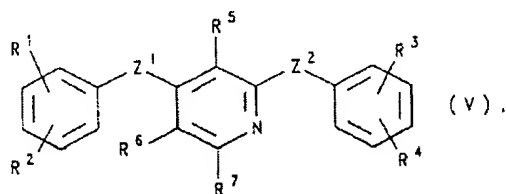
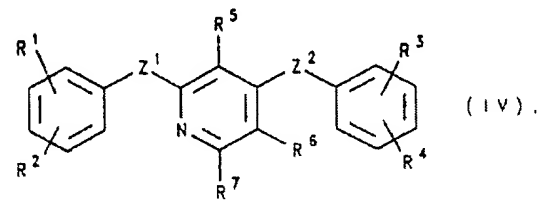
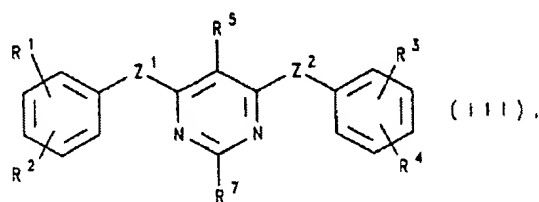
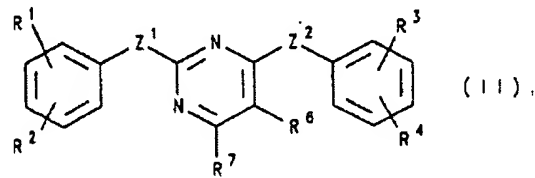
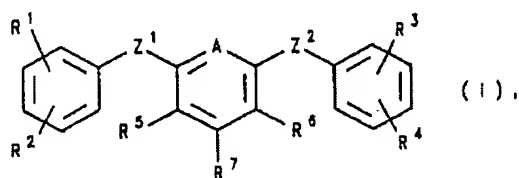
The compounds of the invention, when tested in this assay, demonstrated the
ability to inhibit the clotting of the blood.

* * * * *

25 While the present invention has been described with reference to the specific
embodiments thereof, it should be understood by those skilled in the art that various
changes may be made and equivalents may be substituted without departing from the
true spirit and scope of the invention. In addition, many modifications may be made to
adapt a particular situation, material, composition of matter, process, process step or
30 steps, to the objective, spirit and scope of the present invention. All such modifications
are intended to be within the scope of the claims appended hereto.

WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of the following formulae:



wherein:

A is $-C(R^8)=$ or $-N=$;

Z^1 and Z^2 are independently $-O-$, $-N(R^{12})-$, $-OCH_2-$ or $-S(O)_n$ (where n is 0 to 2);

R^1 and R^4 are each independently hydrogen, halo, alkyl, nitro, $-OR^{12}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{12}$, or $-N(H)S(O)_2R^{15}$;

R^2 is $-C(NH)NH_2$, $-C(NH)N(H)OR^{12}$, $-C(NH)N(H)C(O)OR^{15}$, $-C(NH)N(H)C(O)R^{12}$, $-C(NH)N(H)S(O)_2R^{15}$, or $-C(NH)N(H)C(O)N(H)R^{12}$;

R^3 is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, guanidino, $-OR^{12}$, $-C(NH)NH_2$,

-C(NH)N(H)OR¹², -C(O)N(R¹²)R¹³, -R¹⁴-C(O)N(R¹²)R¹³, -CH(OH)C(O)N(R¹²)R¹³,
 -N(R¹²)R¹³, -R¹⁴-N(R¹²)R¹³, -C(O)OR¹², -R¹⁴-C(O)OR¹², -N(R¹²)C(O)R¹²,
 (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl
 (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by
 alkyl);

R⁵ and R⁶ are independently hydrogen, halo, alkyl, haloalkyl, nitro, -N(R¹²)R¹³,
 -C(O)OR¹², -C(O)N(R¹²)R¹³, -C(O)N(R¹²)CH₂C(O)N(R¹²)R¹³,
 -N(R¹²)C(O)N(R¹²)R¹³, -N(R¹²)C(O)R¹³, -N(R¹²)S(O)₂R¹⁵, or
 -N(R¹²)C(O)N(R¹²)-CH₂C(O)N(R¹²)R¹³;

R⁷ is -S(O)_n-(C(R⁹)(R¹⁰))_m-R¹¹ (where n is 0 to 2 and m is 1 to 4) or
 -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ (where n is 0 to 2 and p is 0 to 4), with the proviso
 that the carbon atom bonded to the sulfur atom in either of these radicals can
 not be bonded to another hetero atom;

R⁸ is hydrogen, alkyl or halo;

each R⁹ is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl,
 cycloalkyl, cycloalkylalkyl, -C(O)OR¹², -R¹⁴-C(O)OR¹², -C(O)N(R¹²)R¹³,
 -R¹⁴-C(O)N(R¹²)R¹³, -C(O)-R¹⁴-N(R¹²)R¹³, -R¹⁴-C(O)-R¹⁴-N(R¹²)R¹³, -C(O)R¹²,
 -R¹⁴-C(O)R¹², -C(O)N(R¹²)N(R¹²)R¹³, -R¹⁴-C(O)N(R¹²)N(R¹²)R¹³,
 -C(R¹²)(OR¹²)-R¹⁴-N(R¹²)(R¹³), -R¹⁴-C(R¹²)(OR¹²)-R¹⁴-N(R¹²)(R¹³),
 -C(R¹²)(OR¹²)C(O)OR¹², -R¹⁴-C(R¹²)(OR¹²)C(O)OR¹², -C(R¹²)(C(O)OR¹²)₂,
 -R¹⁴-C(R¹²)(C(O)OR¹²)₂, -C(R¹²)(N(R¹²)R¹³)C(O)OR¹²,
 -R¹⁴-C(R¹²)(N(R¹²)R¹³)C(O)OR¹², -C(R¹²)(OR¹²)R¹³, -R¹⁴-C(R¹²)(OR¹²)R¹³,
 -N(R¹²)R¹³, -R¹⁴-N(R¹²)R¹³, -N(R¹²)C(O)OR¹⁵, -R¹⁴-N(R¹²)C(O)OR¹⁵,
 -N(R¹²)C(O)R¹³, -R¹⁴-N(R¹²)C(O)R¹³, -N(R¹²)C(NR¹²)R¹⁵,
 -R¹⁴-N(R¹²)C(NR¹²)R¹⁵, -N(R¹²)S(O)₂R¹⁵, -R¹⁴-N(R¹²)S(O)₂R¹⁵,
 -N(R¹²)C(O)N(R¹²)R¹³, -R¹⁴-N(R¹²)C(O)N(R¹²)R¹³, -N(R¹²)C(NR¹²)N(R¹²)R¹³,
 -R¹⁴-N(R¹²)C(NR¹²)N(R¹²)R¹³, -N(R¹²)C(NR¹²)N(R¹²)N(R¹²)R¹³,
 -R¹⁴-N(R¹²)C(NR¹²)N(R¹²)N(R¹²)R¹³, -N(R¹²)-R¹⁴-C(R¹²)(N(R¹²)R¹³)C(O)OR¹²,
 -R¹⁴-N(R¹²)-R¹⁴-C(R¹²)(N(R¹²)R¹³)C(O)OR¹², -N(R¹²)S(O)R¹³,
 -R¹⁴-N(R¹²)S(O)R¹³, -OR¹², -R¹⁴-OR¹², -O-N(R¹²)C(NR¹²)N(R¹²)R¹³,
 -R¹⁴-O-N(R¹²)C(NR¹²)N(R¹²)R¹³, -OS(O)₂OR¹², -R¹⁴-OS(O)₂OR¹²,
 -P(O)(OR¹²)R¹³, -R¹⁴-P(O)(OR¹²)R¹³, -OP(O)(OR¹²)₂, -R¹⁴-OP(O)(OR¹²)₂,
 -P(O)(OR¹²)₂, -R¹⁴-P(O)(OR¹²)₂, -SR¹², -R¹⁴-SR¹², -C(SR¹²)(R¹²)C(O)OR¹²
 (where n is 0 to 2), -R¹⁴-C(SR¹²)(R¹²)C(O)OR¹² (where n is 0 to 2),

- $-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2),
 $-R^{14}-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2),
 $-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$,
 $-SC(O)N(R^{12})R^{13}$, $-R^{14}-SC(O)N(R^{12})R^{13}$, $-SC(S)N(R^{12})R^{13}$, $-R^{14}-SC(S)N(R^{12})R^{13}$,
 $-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)OR^{12}$,
 $-R^{14}-S(O)_2OR^{12}$, $-R^{14}-S(O)_2N(R^{12})R^{13}$, $-R^{14}-S(O)(N(R^{12})R^{13})$;
- or each R^9 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
- or each R^9 is aralkyl (where the aryl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
- or each R^9 is aralkenyl (where the aryl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
- or each R^9 is heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
- or each R^9 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
- or each R^9 is heterocyclylalkenyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl,

halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$;

or each R^9 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

or each R^9 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

each R^{10} is independently hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

or R^9 and R^{10} together form a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$;

R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$;

each R^{12} and R^{13} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{14} is an alkylene or alkylidene chain;

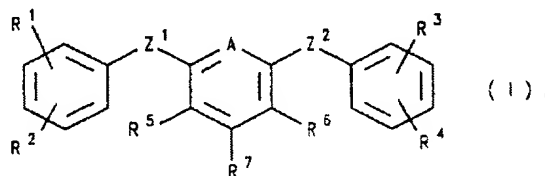
R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and

R^{16} is a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon

atoms may be optionally oxidized and wherein the carbocyclic ring system is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$; or R^{16} is a mono-, bi- or tricyclic heterocyclic ring system containing from 3 to 15 ring members including carbon and 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur atoms, wherein the carbon, nitrogen and sulfur atoms may be optionally oxidized and the nitrogen atoms may be optionally quarternized, and wherein the heterocyclic ring system may be partially or fully saturated or aromatic and is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 selected from formula (I):



as a single stereoisomer or a mixture thereof; or as a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 wherein:

A is $-N=$;

Z^1 and Z^2 are independently $-O-$, $-OCH_2-$ or $-S(O)_n$ (where n is 0 to 2);

R^1 and R^4 are each independently hydrogen, halo or $-OR^{12}$;

R^2 is $-C(NH)NH_2$, $-C(NH)N(H)S(O)_2R^{15}$, or $-C(NH)N(H)C(O)R^{12}$;

R^3 is ureido, guanidino, $-OR^{12}$, $-C(NH)NH_2$, $-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$,

$-N(R^{12})C(O)R^{12}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl),

(1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazoliny (optionally substituted by alkyl);

R^5 and R^6 are independently hydrogen, halo, alkyl, or haloalkyl;

R^7 is $-S(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 to 2 and m is 1 to 4);

each R^9 is independently hydrogen, alkyl, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$,
 $-R^{14}-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, or $-R^{14}-N(R^{12})R^{13}$;

or each R^9 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$,
 $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

or each R^9 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$,
 $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

each R^{10} is independently hydrogen or alkyl;

R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$;

each R^{12} and R^{13} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{14} is an alkylene or alkylidene chain;

R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

4. The compound of Claim 3 wherein:

A is $-N=$;

Z^1 and Z^2 are each $-O-$;

R^1 is hydrogen or $-OR^{12}$;

R^2 is $-C(NH)NH_2$;

R^3 is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by

alkyl);

R^4 is hydrogen;

R^5 and R^6 are each halo;

R^7 is $-S(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 to 2 and m is 1 to 4);

each R^9 is independently hydrogen, alkyl, aryl, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$,
 $-R^{14}-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, or $-R^{14}-N(R^{12})R^{13}$;

each R^{10} is independently hydrogen or alkyl;

R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$;

each R^{12} and R^{13} is independently hydrogen or alkyl;

R^{14} is an alkylene or alkylidene chain;

R^{15} is alkyl or aryl.

5. The compound of Claim 4 wherein:

A is $-N=$;

Z^1 and Z^2 are each $-O-$;

R^1 is hydroxy;

R^2 is $-C(NH)NH_2$;

R^3 is 1-methylimidazol-2-yl or 1-methylimidazolin-2-yl;

R^4 is hydrogen;

R^5 and R^6 are each fluoro;

R^7 is $-S(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 to 2 and m is 1 to 4);

each R^9 is independently hydrogen, alkyl, aryl, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-N(R^{12})R^{13}$,
 or $-R^{14}-N(R^{12})R^{13}$;

each R^{10} is independently hydrogen or alkyl;

R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$;

each R^{12} and R^{13} is independently hydrogen or alkyl;

R^{14} is an alkylene or alkylidene chain;

R^{15} is alkyl or aryl.

6. The compound of Claim 5 selected from the group consisting of:

4-hydroxy-3-[(4-(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-
 3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-methoxycarbonyl)ethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-methoxycarbonylprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(ethoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-ethoxycarbonyl-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-carboxy-3-aminoprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(3-carboxyprop-1-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1,2-dicarboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-carboxyethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1,1-diphenyl-1-carboxymethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(1,1-dimethyl-2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-carboxy-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and

4-hydroxy-3-[(4-(2-ethoxycarbonyl-2-aminoethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

7. The compound of Claim 6, namely 4-hydroxy-3-[(4-

(methoxycarbonylmethyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl]oxy]benzamidine.

8. The compound of Claim 2 wherein:

A is -N=;

Z¹ and Z² are independently -O-, -OCH₂- or -S(O)_n (where n is 0 to 2);

R¹ and R⁴ are each independently hydrogen, halo, alkyl, or -OR¹²;

R² is -C(NH)NH₂, -C(NH)N(H)C(O)R¹², or -C(NH)N(H)S(O)₂R¹⁵;

R³ is ureido, guanidino, -OR¹², -C(NH)NH₂, -C(O)N(R¹²)R¹³, -N(R¹²)R¹³,

(1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazoliny (optionally substituted by alkyl);

R⁵ and R⁶ are independently hydrogen, halo, alkyl, or haloalkyl;

R⁷ is -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ (where n is 0 to 2 and p is 0 to 4);

R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³;

each R¹² and R¹³ is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R¹⁵ is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and

R¹⁶ is a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is substituted by -(C(R¹²)(R¹³))_p-R¹¹ (where p is 0 to 4 and R¹¹ is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, -N(R¹²)R¹³, -C(O)OR¹², or -C(O)N(R¹²)R¹³.

9. The compound of Claim 8 wherein:

A is -N=;

Z¹ and Z² are both -O-;

R¹ is hydrogen or -OR¹²;

R² is -C(NH)NH₂;

R³ is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R⁴ is hydrogen;

R⁵ and R⁶ are each halo;

R⁷ is -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ (where n is 0 to 2 and p is 0);

R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³;

each R¹² and R¹³ is independently hydrogen, alkyl, or aralkyl;

R¹⁶ is a carbocyclic ring system selected from the group consisting of cyclopentyl, cyclohexyl, cyclobutyl, and phenyl, and wherein the ring system is substituted by -(C(R¹²)(R¹³))_p-R¹¹ (where p is 0 to 2 and R¹¹ is defined above), and is optionally substituted by halo, or -C(O)N(R¹²)R¹³.

10. The compound of Claim 9 wherein:

R¹ is hydrogen, hydroxy or benzyloxy;

R³ is 1-methylimidazolin-2-yl;

and R⁵ and R⁶ are both fluoro.

11. The compound of Claim 10 selected from the group consisting of:

4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-aminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-dimethylaminocarbonyl-3-chlorophenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-aminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(4-(2-dimethylaminocarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-(2-carboxyethyl)phenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-(2-ethoxycarbonyl)phenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
 4-hydroxy-3-[(4-(4-carboxyphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and
 4-hydroxy-3-[(4-(4-ethoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

12. The compound of Claim 11, namely, 4-hydroxy-3-[(4-(2-methoxycarbonylphenyl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

13. The compound of Claim 2 wherein:

A is -N=;

Z¹ and Z² are each -O, -S or -OCH₂;

R¹ and R⁴ are independently hydrogen, halo, alkyl or -OR¹²;

R² is -C(NH)NH₂, -C(NH)N(H)C(O)R¹², or -C(NH)N(H)S(O)₂R¹⁵;

R³ is ureido, guanidino, -OR¹², -C(NH)NH₂, -C(O)N(R¹²)R¹³, -N(R¹²)R¹³,

(1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R⁵ and R⁶ are independently hydrogen, halo, alkyl, or haloalkyl;

R⁷ is -S(O)_n-(C(R¹²)(R¹³))_p-R¹⁶ (where n is 0 to 2 and p is 0 to 4);

R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³;

each R¹² and R¹³ is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or

dialkylaminocarbonyl);

R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and

R^{16} is a mono-, bi- or tricyclic heterocyclic ring system containing from 3 to 15 ring members including carbon and 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur atoms, wherein the carbon, nitrogen and sulfur atoms may be optionally oxidized and wherein the heterocyclic ring system may be partially or fully saturated or aromatic and is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$.

14. The compound of Claim 13 wherein:

A is $-N=$;

Z^1 and Z^2 are each $-O$;

R^1 is hydrogen or $-OR^{12}$;

R^2 is $-C(NH)NH_2$;

R^3 is (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 and R^6 are each halo;

R^7 is $-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 to 2 and p is 0 to 4);

R^{11} is $-C(O)OR^{12}$ or $-C(O)N(R^{12})R^{13}$;

each R^{12} and R^{13} is independently hydrogen, alkyl, or aralkyl;

R^{16} is a heterocyclic ring system selected from the group consisting of pyridinyl, imidazolyl, triazinyl, tetrazolyl, and pyrimidinyl, and wherein the heterocyclic ring system is optionally substituted by hydroxy, $-N(R^{12})R^{13}$, or $-C(O)OR^{12}$.

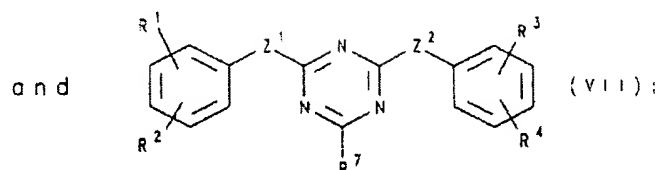
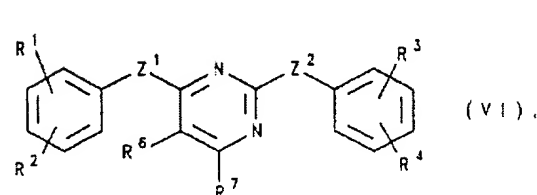
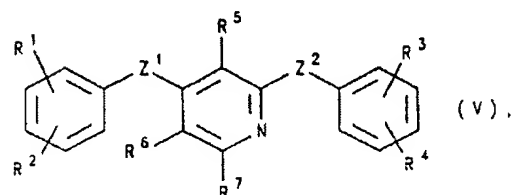
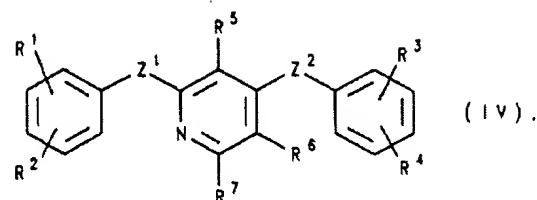
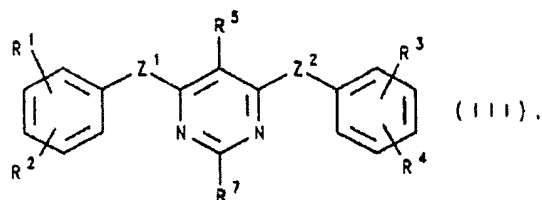
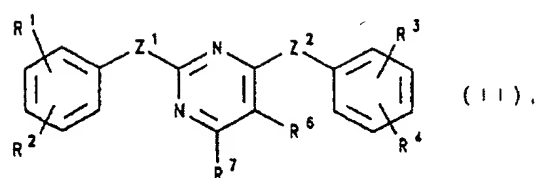
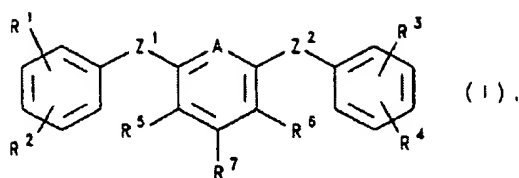
15. The compound of Claim 14 wherein:

R^1 is hydrogen, hydroxy or benzyloxy;

R³ is 1-methylimidazolin-2-yl; and
R⁵ and R⁶ are both fluoro.

16. The compound of Claim 15 selected from the group consisting of:
4-hydroxy-3-[(4-(5-carboxypyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-ethoxycarbonylpyridin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-methyl-5-carboxyimidazol-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(1-methyl-5-methoxycarbonylimidazol-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-hydroxy-6-carboxy-1,2,4-triazol-3-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-hydroxy-6-ethoxycarbonyl-1,2,4-triazol-3-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-amino-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-amino-5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine;
4-hydroxy-3-[(4-(4-hydroxy-5-carboxypyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine; and
4-hydroxy-3-[(4-(4-hydroxy-5-ethoxycarbonylpyrimidin-2-yl)thio-6-(3-(1-methyl)imidazolin-2-yl)phenoxy-3,5-difluoropyridin-2-yl)oxy]benzamidine.

17. A pharmaceutical composition useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound selected from the group consisting of the following formulae:



wherein:

A is $-C(R^8)=$ or $-N=$;

Z^1 and Z^2 are independently $-O-$, $-N(R^{12})-$, $-OCH_2-$ or $-S(O)_n$ (where n is 0 to 2);

R^1 and R^4 are each independently hydrogen, halo, alkyl, nitro, $-OR^{12}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{12}$, or $-N(H)S(O)_2R^{15}$;

R^2 is $-C(NH)NH_2$, $-C(NH)N(H)OR^{12}$, $-C(NH)N(H)C(O)OR^{15}$, $-C(NH)N(H)C(O)R^{12}$, $-C(NH)N(H)S(O)_2R^{15}$, or $-C(NH)N(H)C(O)N(H)R^{12}$;

R^3 is hydrogen, halo, alkyl, haloalkyl, nitro, uraido, guanidino, $-OR^{12}$, $-C(NH)NH_2$, $-C(NH)N(H)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})R^{13}$, $-CH(OH)C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, $-R^{14}-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-N(R^{12})C(O)R^{12}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolyl (optionally substituted by

alkyl);

R^5 and R^6 are independently hydrogen, halo, alkyl, haloalkyl, nitro, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-C(O)N(R^{12})CH_2C(O)N(R^{12})R^{13}$, $-N(R^{12})C(O)N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{13}$, $-N(R^{12})S(O)_2R^{15}$, or $-N(R^{12})C(O)N(R^{12})-CH_2C(O)N(R^{12})R^{13}$;

R^7 is $-S(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 to 2 and m is 1 to 4) or $-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 to 2 and p is 0 to 4), with the proviso that the carbon atom bonded to the sulfur atom in either of these radicals can not be bonded to another hetero atom;

R^8 is hydrogen, alkyl or halo;

each R^9 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})R^{13}$, $-C(O)-R^{14}-N(R^{12})R^{13}$, $-R^{14}-C(O)-R^{14}-N(R^{12})R^{13}$, $-C(O)R^{12}$, $-R^{14}-C(O)R^{12}$, $-C(O)N(R^{12})N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})N(R^{12})R^{13}$, $-C(R^{12})(OR^{12})-R^{14}-N(R^{12})(R^{13})$, $-R^{14}-C(R^{12})(OR^{12})-R^{14}-N(R^{12})(R^{13})$, $-C(R^{12})(OR^{12})C(O)OR^{12}$, $-R^{14}-C(R^{12})(OR^{12})C(O)OR^{12}$, $-C(R^{12})(C(O)OR^{12})_2$, $-R^{14}-C(R^{12})(C(O)OR^{12})_2$, $-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-C(R^{12})(OR^{12})R^{13}$, $-R^{14}-C(R^{12})(OR^{12})R^{13}$, $-N(R^{12})R^{13}$, $-R^{14}-N(R^{12})R^{13}$, $-N(R^{12})C(O)OR^{15}$, $-R^{14}-N(R^{12})C(O)OR^{15}$, $-N(R^{12})C(O)R^{13}$, $-R^{14}-N(R^{12})C(O)R^{13}$, $-N(R^{12})C(NR^{12})R^{15}$, $-R^{14}-N(R^{12})C(NR^{12})R^{15}$, $-N(R^{12})S(O)_2R^{15}$, $-R^{14}-N(R^{12})S(O)_2R^{15}$, $-N(R^{12})C(O)N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(O)N(R^{12})R^{13}$, $-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-N(R^{12})C(NR^{12})N(R^{12})N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(NR^{12})N(R^{12})N(R^{12})R^{13}$, $-N(R^{12})-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-N(R^{12})-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-N(R^{12})S(O)R^{13}$, $-R^{14}-N(R^{12})S(O)R^{13}$, $-OR^{12}$, $-R^{14}-OR^{12}$, $-O-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-R^{14}-O-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-OS(O)_2OR^{12}$, $-R^{14}-OS(O)_2OR^{12}$, $-P(O)(OR^{12})R^{13}$, $-R^{14}-P(O)(OR^{12})R^{13}$, $-OP(O)(OR^{12})_2$, $-R^{14}-OP(O)(OR^{12})_2$, $-P(O)(OR^{12})_2$, $-R^{14}-P(O)(OR^{12})_2$, $-SR^{12}$, $-R^{14}-SR^{12}$, $-C(SR^{12})(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-C(SR^{12})(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2),

$-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$
 (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$,
 $-SC(O)N(R^{12})R^{13}$, $-R^{14}-SC(O)N(R^{12})R^{13}$, $-SC(S)N(R^{12})R^{13}$, $-R^{14}-SC(S)N(R^{12})R^{13}$,
 $-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)OR^{12}$,
 $-R^{14}-S(O)_2OR^{12}$, $-R^{14}-S(O)_2N(R^{12})R^{13}$, $-R^{14}-S(O)(N(R^{12})R^{13})$;

or each R^9 is aryl (optionally substituted by one or more substituents selected from the
 group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$,
 $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$,
 $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

or each R^9 is aralkyl (where the aryl radical is optionally substituted by one or more
 substituents selected from the group consisting of alkyl, halo, haloalkyl,
 haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$,
 $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

or each R^9 is aralkenyl (where the aryl radical is optionally substituted by one or more
 substituents selected from the group consisting of alkyl, halo, haloalkyl,
 haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$,
 $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

or each R^9 is heterocyclyl (optionally substituted by one or more substituents selected
 from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, aralkyl,
 $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$,
 $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);

or each R^9 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted
 by one or more substituents selected from the group consisting of alkyl,
 halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1
 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and
 $-OP(O)(OR^{12})_2$);

or each R^9 is heterocyclylalkenyl (where the heterocyclyl radical is optionally substituted
 by one or more substituents selected from the group consisting of alkyl,
 halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1
 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and
 $-OP(O)(OR^{12})_2$);

or each R^9 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy,

-OR¹², -SR¹², -S(O)_qR¹⁵ (where q is 1 or 2), -C(O)OR¹², -N(R¹²)R¹³,
-C(O)N(R¹²)R¹³, -S(O)₂OR¹² and -OP(O)(OR¹²)₂);

or each R⁹ is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, -OR¹², -SR¹², -S(O)_qR¹⁵ (where q is 1 or 2), -C(O)OR¹², -N(R¹²)R¹³, -C(O)N(R¹²)R¹³, -S(O)₂OR¹² and -OP(O)(OR¹²)₂);

each R¹⁰ is independently hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

or R⁹ and R¹⁰ together form a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, -N(R¹²)R¹³, -C(O)OR¹², or -C(O)N(R¹²)R¹³;

R¹¹ is -C(O)OR¹² or -C(O)N(R¹²)R¹³;

each R¹² and R¹³ is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R¹⁴ is an alkylene or alkylidene chain;

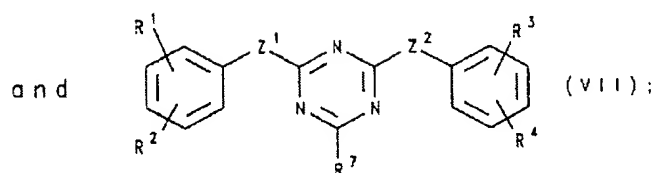
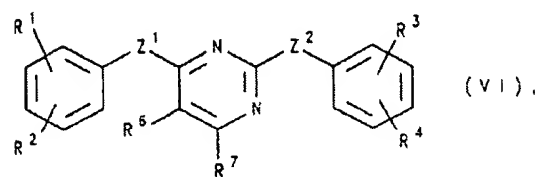
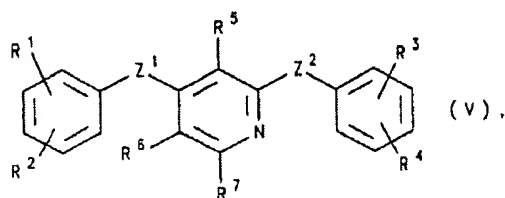
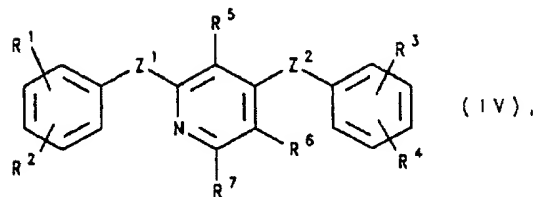
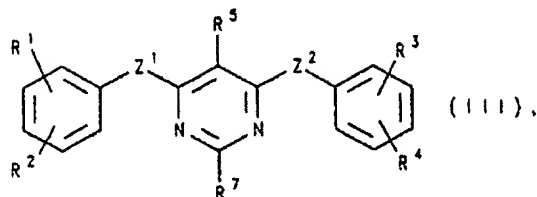
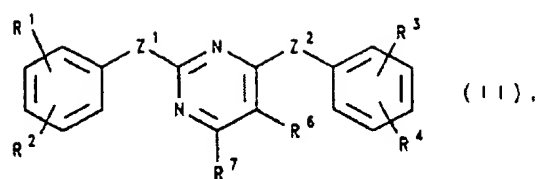
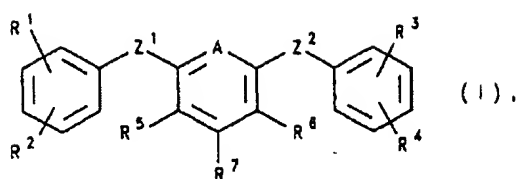
R¹⁵ is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and

R¹⁶ is a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is substituted by -(C(R¹²)(R¹³))_p-R¹¹ (where p is 0 to 4 and R¹¹ is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, -N(R¹²)R¹³, -C(O)OR¹², or -C(O)N(R¹²)R¹³;

or R^{16} is a mono-, bi- or tricyclic heterocyclic ring system containing from 3 to 15 ring members including carbon and 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur atoms, wherein the carbon, nitrogen and sulfur atoms may be optionally oxidized and the nitrogen atoms may be optionally quarternized, and wherein the heterocyclic ring system may be partially or fully saturated or aromatic and is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof thereof, and a pharmaceutically acceptable excipient.

18. A method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound selected from the group consisting of the following formulae:



wherein:

A is $-C(R^8)=$ or $-N=$;

Z^1 and Z^2 are independently $-O-$, $-N(R^{12})-$, $-OCH_2-$ or $-S(O)_n$ (where n is 0 to 2);

R^1 and R^4 are each independently hydrogen, halo, alkyl, nitro, $-OR^{12}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{12}$, or $-N(H)S(O)_2R^{15}$;

R^2 is $-C(NH)NH_2$, $-C(NH)N(H)OR^{12}$, $-C(NH)N(H)C(O)OR^{15}$, $-C(NH)N(H)C(O)R^{12}$, $-C(NH)N(H)S(O)_2R^{15}$, or $-C(NH)N(H)C(O)N(H)R^{12}$;

R^3 is hydrogen, halo, alkyl, haloalkyl, nitro, ureido, guanidino, $-OR^{12}$, $-C(NH)NH_2$, $-C(NH)N(H)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})R^{13}$, $-CH(OH)C(O)N(R^{12})R^{13}$, $-N(R^{12})R^{13}$, $-R^{14}-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-N(R^{12})C(O)R^{12}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 and R^6 are independently hydrogen, halo, alkyl, haloalkyl, nitro, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-C(O)N(R^{12})CH_2C(O)N(R^{12})R^{13}$, $-N(R^{12})C(O)N(R^{12})R^{13}$, $-N(R^{12})C(O)R^{13}$, $-N(R^{12})S(O)_2R^{15}$, or $-N(R^{12})C(O)N(R^{12})-CH_2C(O)N(R^{12})R^{13}$;

R^7 is $-S(O)_n-(C(R^9)(R^{10}))_m-R^{11}$ (where n is 0 to 2 and m is 1 to 4) or $-S(O)_n-(C(R^{12})(R^{13}))_p-R^{16}$ (where n is 0 to 2 and p is 0 to 4), with the proviso that the carbon atom bonded to the sulfur atom in either of these radicals can not be bonded to another hetero atom;

R^8 is hydrogen, alkyl or halo;

each R^9 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, $-C(O)OR^{12}$, $-R^{14}-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})R^{13}$, $-C(O)-R^{14}-N(R^{12})R^{13}$, $-R^{14}-C(O)-R^{14}-N(R^{12})R^{13}$, $-C(O)R^{12}$, $-R^{14}-C(O)R^{12}$, $-C(O)N(R^{12})N(R^{12})R^{13}$, $-R^{14}-C(O)N(R^{12})N(R^{12})R^{13}$, $-C(R^{12})(OR^{12})-R^{14}-N(R^{12})(R^{13})$, $-R^{14}-C(R^{12})(OR^{12})-R^{14}-N(R^{12})(R^{13})$, $-C(R^{12})(OR^{12})C(O)OR^{12}$, $-R^{14}-C(R^{12})(OR^{12})C(O)OR^{12}$, $-C(R^{12})(C(O)OR^{12})_2$, $-R^{14}-C(R^{12})(C(O)OR^{12})_2$, $-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-C(R^{12})(OR^{12})R^{13}$, $-R^{14}-C(R^{12})(OR^{12})R^{13}$, $-N(R^{12})R^{13}$, $-R^{14}-N(R^{12})R^{13}$, $-N(R^{12})C(O)OR^{15}$, $-R^{14}-N(R^{12})C(O)OR^{15}$, $-N(R^{12})C(O)R^{13}$, $-R^{14}-N(R^{12})C(O)R^{13}$, $-N(R^{12})C(NR^{12})R^{15}$, $-R^{14}-N(R^{12})C(NR^{12})R^{15}$, $-N(R^{12})S(O)_2R^{15}$, $-R^{14}-N(R^{12})S(O)_2R^{15}$, $-N(R^{12})C(O)N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(O)N(R^{12})R^{13}$, $-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-N(R^{12})C(NR^{12})N(R^{12})N(R^{12})R^{13}$, $-R^{14}-N(R^{12})C(NR^{12})N(R^{12})N(R^{12})R^{13}$, $-N(R^{12})-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-N(R^{12})-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-N(R^{12})S(O)R^{13}$, $-R^{14}-N(R^{12})S(O)R^{13}$, $-OR^{12}$, $-R^{14}-OR^{12}$, $-O-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-R^{14}-O-N(R^{12})C(NR^{12})N(R^{12})R^{13}$, $-OS(O)_2OR^{12}$, $-R^{14}-OS(O)_2OR^{12}$, $-P(O)(OR^{12})R^{13}$, $-R^{14}-P(O)(OR^{12})R^{13}$, $-OP(O)(OR^{12})_2$, $-R^{14}-OP(O)(OR^{12})_2$, $-P(O)(OR^{12})_2$, $-R^{14}-P(O)(OR^{12})_2$, $-SR^{12}$, $-R^{14}-SR^{12}$, $-C(SR^{12})(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-C(SR^{12})(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})R^{13}$ (where n is 0 to 2), $-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$ (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$ (where n is 0 to 2), $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)OR^{12}$

- (where n is 0 to 2), $-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-R^{14}-S(O)_n-R^{14}-N(R^{12})C(O)R^{12}$ (where n is 0 to 2),
 $-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$, $-R^{14}-S-S-R^{14}-C(R^{12})(N(R^{12})R^{13})C(O)OR^{12}$,
 $-SC(O)N(R^{12})R^{13}$, $-R^{14}-SC(O)N(R^{12})R^{13}$, $-SC(S)N(R^{12})R^{13}$, $-R^{14}-SC(S)N(R^{12})R^{13}$,
 $-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)_qR^{15}$ (where q is 1 or 2), $-R^{14}-S(O)OR^{12}$,
 $-R^{14}-S(O)_2OR^{12}$, $-R^{14}-S(O)_2N(R^{12})R^{13}$, $-R^{14}-S(O)(N(R^{12})R^{13})$;
or each R^9 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
or each R^9 is aralkyl (where the aryl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
or each R^9 is aralkenyl (where the aryl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
or each R^9 is heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, nitro, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
or each R^9 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
or each R^9 is heterocyclylalkenyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$, $-C(O)N(R^{12})R^{13}$, $-S(O)_2OR^{12}$ and $-OP(O)(OR^{12})_2$);
or each R^9 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{12}$, $-SR^{12}$, $-S(O)_qR^{15}$ (where q is 1 or 2), $-C(O)OR^{12}$, $-N(R^{12})R^{13}$,

$-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$;

or each R^9 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{S}(\text{O})_q\text{R}^{15}$ (where q is 1 or 2), $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{OR}^{12}$ and $-\text{OP}(\text{O})(\text{OR}^{12})_2$);

each R^{10} is independently hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

or R^9 and R^{10} together form a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{12}$, or $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$;

R^{11} is $-\text{C}(\text{O})\text{OR}^{12}$ or $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$;

each R^{12} and R^{13} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{14} is an alkylene or alkylidene chain;

R^{15} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and

R^{16} is a mono-, bi- or tricyclic carbocyclic ring system containing from 3 to 15 carbon atoms which may be partially or fully saturated or aromatic, wherein the carbon atoms may be optionally oxidized and wherein the carbocyclic ring system is substituted by $-(\text{C}(\text{R}^{12})(\text{R}^{13}))_p-\text{R}^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-\text{N}(\text{R}^{12})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{12}$, or $-\text{C}(\text{O})\text{N}(\text{R}^{12})\text{R}^{13}$;

or R^{16} is a mono-, bi- or tricyclic heterocyclic ring system containing from 3 to 15 ring

members including carbon and 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur atoms, wherein the carbon, nitrogen and sulfur atoms may be optionally oxidized and the nitrogen atoms may be optionally quarternized, and wherein the heterocyclic ring system may be partially or fully saturated or aromatic and is substituted by $-(C(R^{12})(R^{13}))_p-R^{11}$ (where p is 0 to 4 and R^{11} is defined above), and is optionally substituted by alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, halo, haloalkyl, haloalkoxy, hydroxy, $-N(R^{12})R^{13}$, $-C(O)OR^{12}$, or $-C(O)N(R^{12})R^{13}$;

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05231

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/12 C07D401/14 A61K31/44 //(C07D401/12,233:00,
213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 28427 A (BERLEX LAB ;BUCKMAN BRAD O (US); DAVEY DAVID D (US); GUILFORD WILL) 19 September 1996 see claims	1,17
A,P	WO 97 29067 A (BERLEX LAB) 14 August 1997 see claims	
A	EP 0 540 051 A (DAIICHI SEIYAKU CO) 5 May 1993 cited in the application see abstract; claims	1,17
A	WO 92 08709 A (PENTAPHARM AG) 29 May 1992 see abstract	1,17
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

14 January 1998

Date of mailing of the international search report

30.01.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Frelon, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GERATZ J D ET AL: "NOVEL BIS(BENZAMIDINO) COMPOUNDS WITH AN AROMATIC CENTRAL LINK INHIBITORS OF THROMBIN, PANCREATIC KALLIKREIN, 1 TRYPSIN, AND COMPLEMENT" JOURNAL OF MEDICINAL CHEMISTRY, vol. 19, no. 5, 1 May 1976, pages 634-639, XP000573915 see the whole document</p> <p>---</p>	1,17
A	<p>GERATZ J D ET AL: "THE INHIBITION OF UROKINASE BY AROMATIC DIAMIDINES" THROMBOSIS ET DIATHESIS HAEMORRHAGICA, vol. 33, no. 2, 30 April 1975, pages 230-243, XP000574202 see claims 45-51; table 2</p> <p>---</p>	1,17
A	<p>CHAUHAN P M S ET AL: "EFFECT OF NEW DIAMIDINES AGAINST LEISHMANIA DONOVANI INFECTION" INDIAN JOURNAL OF EXPERIMENTAL BIOLOGY, vol. 31, no. 2, 1 February 1993, pages 196-198, XP000573781 see the whole document</p> <p>---</p>	1,17
A	<p>TIDWELL R R ET AL: "STRATEGIES FOR ANTICOAGULATION WITH SYNTHETIC PROTEASE INHIBITORS XA INHIBITORS VERSUS THROMBIN INHIBITORS" THROMBOSIS RESEARCH, vol. 19, no. 3, 1 August 1980, pages 339-349, XP000574196 cited in the application see the whole document</p> <p>-----</p>	1,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/05231

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1-17

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The huge number of theoretically conceivable compounds resulting from the combinations of all the claimed substituent definitions prevents the search from being carried out comprehensively. It is noted that the examples illustrate the claimed invention for a specific range of values. Additionally such uncertainties on the claimed scope may introduce contradictions and render the unity questionable. Guided by the description, the search has been based on the illustration of the given examples (Art. 83, 84 EPC; Rule 45 EPC).

Remark : Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/05231

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